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LYMPHOMA WORKSHOP BOOK



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Contents

Committees.....	1
LYMPHOMA SESSION I Unusual cases of classical Hodgkin lymphoma, including lymphocyte-rich classic Hodgkin-lymphoma (CHL) and lymphocyte-depleted CHL, CD30 negative CHL, CHL with cytotoxic phenotype, T-follicular helper (TFH)-cell rich	3
LYMPHOMA SESSION II B-cell lymphomas with prominent histiocytes, e.g. T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), THRLBCL-like lymphomas including Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL) and nodular lymphocyte -predominant Hodgkin lymphoma/ nodular lymphocyte predominant B-cell lymphoma (NLPHL/NLPBL) pattern E, other aggressive or small B-cell lymphomas with granulomatous reaction	101
LYMPHOMA SESSION III Immune privileged site lymphomas excluding primary diffuse large B-cell lymphoma (DLBCL) of the brain parenchyma and testis (i.e. primary lymphomas of the ovary, adrenal gland, breast, meninges).....	200
LYMPHOMA SESSION IV Nodal and extranodal T-cell lymphomas with prominent histiocytes, e.g. Lennert lymphoma, anaplastic large cell lymphoma (ALCL), associated with haemophagocytic lymphohistiocytosis (HLH); excluding cutaneous lymphoma	254
LYMPHOMA SESSION V Primary mucosal or cutaneous CD30+ T-cell lymphoma/lymphoproliferative disorders (LPDs); incl. lymphomatoid papulosis (LYP), cutaneous anaplastic large cell lymphoma (ALCL)	337

LYMPHOMA SESSION I | Unusual cases of classical Hodgkin lymphoma, including lymphocyte-rich classic Hodgkin-lymphoma (CHL) and lymphocyte-depleted CHL, CD30 negative CHL, CHL with cytotoxic phenotype, T-follicular helper (TFH)-cell rich

EA4HP26-LYWS-3	Lymphocyte-depleted classic Hodgkin lymphoma arising in a patient with an inborn error of immunity
EA4HP26-LYWS-6	Syncytial variant of nodular sclerosis classical Hodgkin lymphoma with aberrant expression of T-cell antigens
EA4HP26-LYWS-8	A case of chronic lymphocytic leukemia/small lymphocytic lymphoma transforming into classic Hodgkin lymphoma
EA4HP26-LYWS-17	Synchronous Interfollicular Classic Hodgkin Lymphoma and a B-cell Lymphoproliferative Disorder in a Patient with <i>CTLA4</i> Haploinsufficiency
EA4HP26-LYWS-18	Septic-like Presentation Unmasking a Rare Lymphocyte-depleted Subtype of Classic Hodgkin Lymphoma
EA4HP26-LYWS-24	Adult T-cell leukemia/lymphoma with HTLV-1-infected HRS-like cells (ATLL-HH)
EA4HP26-LYWS-28	EBV positive classic Hodgkin lymphoma with cytotoxic molecule expression and a concurrent small T-cell clone of uncertain significance
EA4HP26-LYWS-41	Classical Hodgkin lymphoma, mixed cellularity type with expression of cytotoxic granules.
EA4HP26-LYWS-47	CD30 negative classic Hodgkin lymphoma with granulomatous background in a patient with history of marginal zone lymphoma
EA4HP26-LYWS-54	Classical Hodgkin's lymphoma with marked granulomatous reaction mimicking sarcoidosis
EA4HP26-LYWS-58	EBV-positive lymphocyte-rich classic Hodgkin lymphoma
EA4HP26-LYWS-59	Classic Hodgkin Lymphoma, "essentially" CD30 (BerH2) negative
EA4HP26-LYWS-65	Classical Hodgkin lymphoma with an unusual blast-rich growth pattern
EA4HP26-LYWS-67	High-risk lymphocyte-rich classic Hodgkin lymphoma presenting in a young man
EA4HP26-LYWS-82	Mediastinal grey zone lymphoma: A microenvironment-rich tumor and a diagnostic challenge
EA4HP26-LYWS-87	Composite classic Hodgkin lymphoma and Rosai-Dorfman disease
EA4HP26-LYWS-89	CD30 negative classic Hodgkin lymphoma
EA4HP26-LYWS-96	An unusual presentation of an unusual variant of classic Hodgkin lymphoma
EA4HP26-LYWS-97	Classic Hodgkin Lymphoma, CD30-negative
EA4HP26-LYWS-111	PAX5-negativity in classic Hodgkin lymphoma - does it exist?
EA4HP26-LYWS-116	Hodgkin-Type Richter Transformation, an uncommon evolution of CLL/SLL - a short case series
EA4HP26-LYWS-120	Nodular sclerosis classic Hodgkin lymphoma with cytotoxic phenotype
EA4HP26-LYWS-124	Classic Hodgkin Lymphoma masked by non-necrotizing granulomatous inflammation with multinucleated giant cells
EA4HP26-LYWS-128	Classical Hodgkin Lymphoma, Nodular Sclerosis Type (rare CD30-negative variant)

EA4HP26-LYWS-129	EBV+ DLBCL versus Hodgkin's lymphoma
EA4HP26-LYWS-131	Classic Hodgkin lymphoma, lymphocyte-rich variant with TFH cell enriched background
EA4HP26-LYWS-147	Classic Hodgkin lymphoma with a predominantly germinotropic pattern
EA4HP26-LYWS-152	Classic Hodgkin Lymphoma in a background of follicular helper T cells.
EA4HP26-LYWS-167	Relapsed Classical Hodgkin Lymphoma With Aberrant Cytotoxic Marker Expression
EA4HP26-LYWS-172	Classic Hodgkin lymphoma with interfollicular pattern and Castleman-like features
EA4HP26-LYWS-182	A case of MAL1+ Diffuse Large B-Cell Lymphoma arising in an eosinophil, T-cell and histiocyte rich background
EA4HP26-LYWS-189	38-year-old HIV patient with classic Hodgkin lymphoma (cHL) associated with fulminant hemophagocytic lymphohistiocytosis (HLH)
EA4HP26-LYWS-194	Classic Hodgkin lymphoma with aberrant T-cell antigen expression
EA4HP26-LYWS-196	CD30(+) Lymphoproliferative Neoplasm with T- and B-cell Antigen Expression
EA4HP26-LYWS-201	A different "gray zone": a borderline case of lymphocyte-rich classic Hodgkin lymphoma versus nodular lymphocyte-predominant Hodgkin lymphoma
EA4HP26-LYWS-204	TFH-rich classic Hodgkin lymphoma
EA4HP26-LYWS-212	A CD30 negative nodular sclerosis classic Hodgkin lymphoma
EA4HP26-LYWS-214	Peripheral T-cell lymphoma NOS, TFH phenotypewith Hodgkin and Reed-Sternberg-like cells
EA4HP26-LYWS-231	Epstein-Barr virus (EBV) associated lymphoid proliferation with overlapping features of classic Hodgkin lymphoma and chronic EBV-positive lymphoid cell proliferation
EA4HP26-LYWS-236	Classic Hodgkin Lymphoma with Cytotoxic Phenotype
EA4HP26-LYWS-237	Classic Hodgkin Lymphoma with Unusual Histomorphology
EA4HP26-LYWS-242	An unusual case of classic Hodgkin lymphoma expressing cytotoxic molecules
EA4HP26-LYWS-254	<i>Lymphocyte-rich classic Hodgkin lymphoma</i>
EA4HP26-LYWS-255	An unusual variant of classic Hodgkin lymphoma
EA4HP26-LYWS-262	Unusual case of classic Hodgkin lymphoma with features of lymphocyte-depleted subtype.
EA4HP26-LYWS-270	Classic Hodgkin Lymphoma with Aberrant Expression of T-Cell Markers
EA4HP26-LYWS-281	Post-treatment Classic Hodgkin lymphoma with TIA-1(+) cells
EA4HP26-LYWS-282	#282 Lymphadenopathy with a history of AITL
EA4HP26-LYWS-287	Classic Hodgkin lymphoma with concomitant low grade B cell lymphoma and follicular helper T cell proliferation
EA4HP26-LYWS-302	A wolf in sheep's clothing: multiply refractory lymphocyte-rich classic Hodgkin lymphoma
EA4HP26-LYWS-303	EBV(+) lymphoma with Reed-Sternberg cells and numerous atypical T-cells with a T-follicular helper immunophenotype, favor nodular sclerosis-type classic Hodgkin lymphoma.
EA4HP26-LYWS-310	Lymphoma with morphologic findings in favor of a diagnosis of lymphocyte-depleted classic Hodgkin lymphoma and clonality studies identifying clonal TRG rearrangement

EA4HP26-LYWS-317	Lymphocyte-Rich Classic Hodgkin Lymphoma: The Subtype That Whispers
EA4HP26-LYWS-320	Classic Hodgkin lymphoma preceded by a lymphoproliferative disorder featuring Hodgkin/Reed-Sternberg-like cells.
EA4HP26-LYWS-337	Classic Hodgkin lymphoma with T follicular helper rich background or TFH lymphoma
EA4HP26-LYWS-343	Classic Hodgkin lymphoma, with aberrant expression of T- cell markers.
EA4HP26-LYWS-353	CD30 positive lymphoma consistent with Classical Hodgkin lymphoma with syncitial growth pattern, extensive necrosis, aberrant expression of T cell markers and LCA
EA4HP26-LYWS-354	Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL)
EA4HP26-LYWS-356	Nodular lymphocytic predominant Hodgkin lymphoma in a lymphatic malformation
EA4HP26-LYWS-365	EBV+ lymphocyte rich classic Hodgkin lymphoma with extensive granulomatous reaction and abundant Tfh T-cells; diagnostic challenges in distinction from nodular lymphocyte predominant Hodgkin lymphoma.
EA4HP26-LYWS-370	Classic Hodgkin Lymphoma in an immunosuppressed patient with disseminated <i>Mycobacterium genavense</i> infection
EA4HP26-LYWS-382	Stage IV lymphocyte-rich classic Hodgkin lymphoma presents in young female with cardiac and B symptoms.
EA4HP26-LYWS-384	Classic Hodgkin lymphoma with necrotizing granuloma
EA4HP26-LYWS-385	PRIMARY EXTRANODAL LYMPHOCYTE RICH CLASSICAL HODGKIN LYMPHOMA INVOLVING NASOPHARYNX
EA4HP26-LYWS-386	Atypical CD30+, EBV+ B-cells in a background of lymphohistiocytic infiltrate
EA4HP26-LYWS-390	Lymphocyte Rich Classic Hodgkin Lymphoma: ask for excision biopsy.
EA4HP26-LYWS-412	Concealed Primary Bone Marrow Hodgkin Lymphoma with extensive Histiocytic Infiltration, Hemophagocytic Lymphohistiocytosis and acute fatal course
EA4HP26-LYWS-415	Extranodal Classic Hodgkin Lymphoma of Maxillary Sinus
EA4HP26-LYWS-418	An unusual case of classic Hodgkin lymphoma with partial CD30 expression
EA4HP26-LYWS-422	A Challenging Case of a High-Grade CD30-positive Lymphoma
EA4HP26-LYWS-428	Does extra-mediastinal Grey Zone Lymphoma exist ?
EA4HP26-LYWS-433	Cytotoxic marker-positive classic Hodgkin Lymphoma, EBV negative, in an autoimmune/therapy-related setting.
EA4HP26-LYWS-434	Challenging diagnosis of a classic Hodgkin lymphoma, lymphocyte rich subtype
EA4HP26-LYWS-440	A difficult case of an EBV-positive lymphoproliferative disorder in the lung
EA4HP26-LYWS-443	An Unusual Recurrent/Relapsing Case of EBV+ Classic Hodgkin Lymphoma
EA4HP26-LYWS-444	<i>A case of lymphocyte rich classic Hodgkin lymphoma in a patient with an underlying/concomitant autoimmune disorder.</i>
EA4HP26-LYWS-447	Classic Hodgkin Lymphoma, EBV-Positive, arising in Immune Deficiency/Dysregulation
EA4HP26-LYWS-448	Unusual EBV-positive lymphoproliferative disorder abundant epithelioid histiocytes and overlapping features of nTFH-AI and CHL
EA4HP26-LYWS-450	Mediastinal Gray Zone Lymphoma with Genetic Double Hit (IGH::BCL2 + MYC)

Lymphocyte-depleted classic Hodgkin lymphoma arising in a patient with an inborn error of immunity

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Case Description

A 9-year-old boy with a history of a T-cell defect (CD4 lymphopenia with adequate mitogen responses) and hypogammaglobulinemia with undetectable IgA on antibiotic prophylaxis presented with two weeks of fever, EBV viremia, productive cough, decreased appetite, diarrhea, and fatigue. He was found to have pneumonia and *C. difficile* on admission. Imaging demonstrated bulky lymphadenopathy, hepatosplenomegaly with hypoattenuating foci, and bilateral pulmonary nodules. An incisional lymph node biopsy and a needle biopsy of the liver were performed.

Biopsy Fixation Details

The specimens were fixed in 10% neutral buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

Histologic sections of both samples demonstrated an abnormal diffuse cellular infiltrate composed of a predominance of large, highly pleomorphic and multinucleated cells with large nucleoli compatible with Hodgkin/Reed-Sternberg cells surrounded by histiocytes and sparse lymphocytes, consistent with a reticular/anaplastic histologic pattern.

Immunophenotype

Flow cytometry of the lymph node and the liver biopsies was negative for an abnormal T-cell or B-cell population. By immunohistochemistry, the large cells expressed CD30, PAX5 (weak), CD20 (weak, small subset), CD79a (weak, diffuse), OCT2 (weak), MUM1, and CD15 (subset). They were negative for CD3, ALK1, CD34, CD56, cytokeratin AE1/AE3, myeloperoxidase, CD117, CD45, and BOB1. Dual ultrasensitive chromogenic in situ hybridization (CISH) for kappa and lambda light chain-encoding mRNA showed polytypic plasma cells and was negative in the large cells. In situ hybridization for EBER was positive in the large cells. The large cells were positive for LMP1 and negative for EBNA2, consistent with a type II latency pattern. CD68 and CD163 highlighted histiocytes without abnormal expression of CD1a or S100.

Cytogenetics

Not performed.

Molecular Studies

Molecular testing was not performed on the surgical pathology specimens.

Proposed Diagnosis

Epstein-Barr virus-positive classic Hodgkin lymphoma (CHL), lymphocyte-depleted subtype (ICC 2022).

Epstein-Barr virus-positive classic Hodgkin lymphoma, lymphocyte-depleted subtype, DNA ligase IV deficiency (WHO 5th ed.).

Interesting Feature(s)

Subsequent to the diagnosis of classic Hodgkin lymphoma (CHL), additional testing for the underlying immune defect was performed. Germline genetic testing revealed two variants in *LIG4* (*LIG4*: p.Ser504Pro and p.Asp275His). A DNA repair assessment in lymphocytes (T, B, NK) by flow cytometry performed on blood identified normal mobilization of the DNA-double-stranded-break (DSB) repair pathway at 1h post-irradiation (IR) but defective DNA-DSB repair at 24h post-IR, which is the pattern typically observed in radiosensitive SCID, including DNA ligase IV deficiency. This disorder is a rare autosomal recessive condition that impairs the non-homologous end-joining mechanism involved

in double-stranded DNA breaks and can manifest with bird-like facies, developmental delay, sensitivity to ionizing radiation, recurrent infections (due to impaired B-cell and T-cell receptor development during VDJ recombination), and an increased risk of hematologic malignancy. While lymphocyte-depleted CHL is very rare, it is more commonly seen in the setting of immunodeficiency. Interestingly, this tumor demonstrated a type II EBV latency pattern, typical of CHL, rather than a type III latency pattern that is more often seen in the setting of immunodeficiency and also was diagnosed in the setting of EBV viremia. The patient received 5 cycles of BV-ABV-PC with a complete metabolic response with plans for future bone marrow transplant.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-positive) lymphocyte-depleted, DNA ligase deficiency

EA4HP26-LYWS-6

Syncytial variant of nodular sclerosis classical Hodgkin lymphoma with aberrant expression of T-cell antigens

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Case Description

The patient is a 21-year-old man with no significant past medical history who presented with enlarged right neck lymph node (LN). PET/CT showed cervical, supraclavicular, mediastinal, and abdominal lymphadenopathy. A complete blood cell count showed white blood cell 5.8 K/uL, hemoglobin 14.5 g/dL, and platelets 197 K/uL with 60% neutrophils, 23% lymphocytes, 10% monocytes, and 7% eosinophils. Lactate dehydrogenase (125 U/L) and beta 2 microglobulin (1.6 mg/L) were within normal range. Cervical LN biopsy showed syncytial variant of nodular sclerosis classical Hodgkin lymphoma (CHL) with expression of T cell antigens. A bone marrow biopsy was negative for lymphoma involvement. The patient is currently treated with Nivolumab, doxorubicin, vinblastine, and dacarbazine.

Biopsy Fixation Details

The LN core biopsy was fixed in formalin

Frozen Tissue Available

The LN core biopsy was fixed in formalin

Details of Microscopic Findings

Histologic sections show needle-shaped fragments of lymphoid tissue with broad fibrous band and confluent clusters of large pleomorphic cells with prominent nucleoli and abundant cytoplasm in a background of predominantly small lymphocytes, occasional eosinophils, plasma cells, and histiocytes. Foci of necrosis is noted.

Immunophenotype

Immunostains show that the large lymphoma cells are positive for CD30, CD15 (subset), PAX5, MUM-1, BCL6, CD3 (subset), CD4 (subset), CD5 (subset), CD7 (subset), and negative for CD10, CD20, CD79a, BOB1, OCT2, ALK-1, TIA-1, granzyme B. Ki-67 highlights the large cells, which represent ~30% of all cells focally. In situ hybridization for EBV (EBER) is negative.

Flow cytometry analysis did not detect a definite aberrant T cell population.

Cytogenetics

45~47,XY,del(3)(p25p14)[cp3]/46,XY[17].

FISH was negative for *MYC* rearrangement.

Molecular Studies

No monoclonal IGH or TCR beta or gamma gene rearrangement was detected by PCR.

Next generation sequencing (NGS) using a panel of 162 genes was negative for mutation.

Proposed Diagnosis

Syncytial variant of nodular sclerosis CHL with aberrant expression of T-cell antigens

Interesting Feature(s)

Cases of CHL with aberrant T-cell antigen expression are rare and pose a diagnostic challenge. The differential diagnoses include CHL, nodular sclerosis, synovial variant with expression of T cell antigens vs ALK-negative anaplastic large cell lymphoma (ALCL). Features in favor of CHL include PAX5 expression and absence of monoclonal TCR rearrangement, ALCL-related rearrangement and cytotoxic markers. Features in favor of ALCL include expression of multiple T-cell markers. Overall, a diagnosis of CHL with T-cell antigen expression is favored. Follow-up data is not yet available due to the recent timing of his diagnosis. However, CHL with T-cell antigen expression are frequently associated with nodular sclerosis histology and have been reported to exhibit significantly shorter overall survival and event-free survival.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-negative) with partial expression of T-cell characteristic antigens
No subtyping in core biopsies advisable

EA4HP26-LYWS-8

A case of chronic lymphocytic leukemia/small lymphocytic lymphoma transforming into classic Hodgkin lymphoma

Dr. Tamara Pikivaca¹, Dr. Anamarija Perry²

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Case Description

The patient is an 85-year-old man, diagnosed with chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) with diffuse lymphadenopathy and bone marrow involvement 4 years prior to this biopsy. He was treated with acalabrutinib, obinutuzumab and venetoclax with a history of noncompliance and discontinued medication against medical advice. The last CT scan of the neck was done approximately 8 months before the current biopsy, and it showed progression of the disease in multiple lymph node sites in comparison with previous CT scan three years ago. The patient was put on acalabrutinib with good clinical response and significantly decreased peripheral lymphadenopathy in the neck and axillary region. However, there was a residual markedly enlarged lymph node in the right neck and excisional biopsy of was performed to rule out a Richter transformation.

Biopsy Fixation Details

Formalin-fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Sections show lymph node with completely effaced architecture by an atypical lymphoid infiltrate in a diffuse and vaguely nodular patterns. Lymph node is effaced by CLL/SLL composed of sheets of lymphoma cells that are small with round to slightly irregular nuclei, clumped chromatin, inconspicuous nucleoli, and scant cytoplasm. Proliferation centers, composed of prolymphocytes and occasional paraimmunoblasts, are seen. Large area of the lymph node is vaguely demarcated from the rest of the node, and it shows numerous scattered Hodgkin/Reed-Sternberg (HRS) cells in a background of CLL/SLL, in addition to histiocytes and occasional eosinophils.

Immunophenotype

The CLL/SLL cells are positive for CD20, PAX5, CD5, CD23 (weak), and CD45 and are negative for cyclin D1. The HRS cells are positive for PAX5 (weak), CD30, CD15, MUM1, and are negative for CD20 and CD45. In situ hybridization for EBV-encoded RNA (EBER-ISH) is negative.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with transformation to classic Hodgkin lymphoma (CHL).

Interesting Feature(s)

This is an example of CLL/SLL with an area of transformation to classic Hodgkin lymphoma. Although there are still numerous CLL/SLL cells in the area where HRS cells are seen, these areas also show other inflammatory cells and vague demarcation from rest of the lymph node, sufficient for diagnosis of CHL, and consistent with Richter transformation. The clinical significance of CLL/SLL with isolated HRS cells versus an overt transformation of CLL/SLL to CHL is incompletely understood. However, some studies showed that the prognosis is similar and both groups of patients may benefit from Hodgkin-directed therapy.

References:

1. King RL, Gupta A, Kurtin PJ, Ding W, Call TG, Rabe KG, Kenderian SS, Leis JF, Wang Y, Schwager SM, Slager SL, Kay NE, Koehler A, Ansell SM, Inwards DJ, Habermann TM, Shi M, Hanson CA, Howard MT, Parikh SA. Chronic lymphocytic leukemia (CLL) with Reed-Sternberg-like cells vs Classic Hodgkin lymphoma transformation of CLL: does this distinction matter? *Blood Cancer J.* 2022 Jan 28;12(1):18. doi: 10.1038/s41408-022-00616-6. PMID: 35091549; PMCID: PMC8799721.

Panel Diagnosis: Hodgkin variant of Richter transformation

EA4HP26-LYWS-17

Synchronous Interfollicular Classic Hodgkin Lymphoma and a B-cell Lymphoproliferative Disorder in a Patient with *CTLA4* Haploinsufficiency

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Case Description

An eleven-year-old male presented with a 3-week history of bilateral lymph node enlargement and ear drainage. The patient had a history of chronic small stature (131 cm and 24 kg, < 1%), molluscum, chronic otitis media, lymphopenia (absolute lymphocyte count = 0.55 K/mcL), and significant family history of autoimmunity. Ultrasound and subsequent CT scan revealed a 4.5 x 1.9 x 3.2 cm right sided posterior neck mass along with a left sided 2.2 x 0.6 x 1.7 cm left neck mass. The CT scan also found multiple bilateral pulmonary nodules, many of which were calcified.

Infectious workup, DOCK8 deficiency, iNKT percentage, AP (XLP1) and XIAP (XLP2) studies were normal. EBV qPCR (blood): 750 There were decreased proportions of naive CD4+ and CD8+ T-cells.

After the diagnosis of the neck mass was rendered, one of the lung nodules was biopsied for staging purposes.

The whole exome sequencing results came back a few days later.

Biopsy Fixation Details

Neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Examination of the lymph node shows a partially effaced architecture with follicular hyperplasia. Between the follicles are occasional large to intermediate sized atypical cells with prominent nucleoli and occasional Reed-Sternberg morphology. Most of the background cells consist of small lymphocytes, immunoblasts, plasma cells, and a few epithelioid histiocytes. Neutrophils and eosinophils are not readily identified. The capsule is slightly thickened and there are only rare areas of fibrosis.

Immunophenotype

By immunohistochemistry, the large, atypical cells express CD30, focal CD15, dim PAX-5, MUM-1, and weak CD79a. They are negative for CD20, BCL-6, and ALK-1. The atypical cells are positive for EBV by in situ hybridization (EBER).

Cytogenetics

None performed

Molecular Studies

Rapid whole genomic sequencing revealed a heterozygous variant c.151 C>Tp.(R51*) of *CTLA4*

Proposed Diagnosis

Classic Hodgkin lymphoma, interfollicular variant, EBV positive secondary to *CTLA4* haploinsufficiency

Interesting Feature(s)

Interfollicular variant of classic Hodgkin lymphoma (CHL) is a rare morphologic pattern typically associated with mixed cellularity CHL. Diagnosis requires a high level of suspicion since it can be mistaken for reactive hyperplasia and could be easily missed on a needle core biopsy.

42 cases reported from 1983 to 2024: •26 (61.9%) in children up to 18 years and 9 (21.4%) in young adults (19 - 40 years)

•Of the 13 cases with adequate clinical information on follow up: 11 cases (76.9%) went into complete remission or showed no recurrence.

•Majority of cases have localized cervical lymphadenopathy

CTLA4 Haploinsufficiency increases the risk for cancer: •The two most common cancers are CHL and gastric adenocarcinoma

•More than half of the cancers are EBV-associated

•*CTLA4* haploinsufficiency may predispose the patient to CHL due to disrupted T-cell-related mechanism

The lung lesion was biopsied one month after the neck biopsy. There were large cells in the atypical aggregate that expressed strong CD20 and CD79a. These cells were negative for EBER and CD15. The patient's original CHL in the neck expressed EBER, CD30, focal CD15, and weak CD79a. CD30 highlights numerous immunoblasts. The proliferation seen in this biopsy also included numerous plasma cells which are lambda restricted and EBER positive. Of note, the neck node plasma cells were polyclonal and EBER negative.

Given the underlying *CTLA4* haploinsufficiency, these findings were consistent with an EBV positive, polymorphous lymphoproliferative disorder.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV positive) mixed cellularity in a particular clinical *CTLA4* haploinsufficiency

Septic-like Presentation Unmasking a Rare Lymphocyte-depleted Subtype of Classic Hodgkin Lymphoma

Dr. Raniah Alamri, Dr. Nouf Hijazi, Dr. Leena Taher, Dr. Saeed Al Sheiban

King Abdulaziz Medical City, National Guard Health Affairs, Pathology, Riyadh, Saudi Arabia

Case Description

A 73-year-old woman with a history of hypertension, cardiomyopathy, and hypothyroidism, who was admitted with fever, poor appetite, and epigastric pain for 3 months. She had a history of sick contact and was recently tested positive for COVID-19. Her CBC showed anemia and thrombocytopenia; WBCs $7.7 \times 10^9/L$, Hgb 85 gm/L and Plt $27 \times 10^9/L$ along with elevated inflammatory markers (PCT, ESR) and lactic acidosis. Qualitative PCR was positive for Herpes simplex virus-1 (HSV-1). Chest X-ray showed bilateral loculated pleural effusions. While abdominal and pelvic CT scan revealed multiple focal hypodense splenic lesions, an enlarged hepatic cystic lesion (0.5 cm), and mild free ascitic fluid, along with mild perisplenic and mesenteric lymphadenopathy (~0.9 cm), the findings were suggestive of an infectious process with abscess formation. The patient was started on antibiotics; but no clinical improvement was observed. Blood and urine cultures were negative. A follow-up abdominal CT showed rapid interval enlargement of the hepatic, splenic, and mesenteric lymph nodes, with multiple suspicious bilateral cervical and supraclavicular lymph nodes (~3-4 cm) subsequently identified on neck ultrasonography. An excisional biopsy of the right cervical lymph node was performed revealing Classic Hodgkin lymphoma, lymphocyte-depleted subtype, EBV+. Consequently, the patient was started on chemotherapy but expired soon after.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The histologic sections of the right cervical lymph node revealed many large atypical cells with bizarre nuclei and prominent nucleoli with a subset of Reed-Sternberg cells that were present in a fibrotic background rich in histocytes and moderately few small lymphocytes.

Immunophenotype

The atypical cells expressed CD30, CD15, MUM1, and dim PAX5, while negative for CD20, CD79A, BOB-1, OCT2, CD3, CD5, CD10, BCL2, and BCL6. ALK, and Pancytokeratin were negative. CD68 highlighted many histocytes in the background and EBER was positive in many of the large cells.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Septic-like Presentation Unmasking a Rare Lymphocyte-depleted Subtype of Classic Hodgkin Lymphoma.

Interesting Feature(s)

Lymphocyte-depleted classical Hodgkin lymphoma (LD-CHL) is the rarest form of CHL, accounting for less than 2% of cases. It is typically associated with advanced-stage disease and has a poor prognosis, and is often linked to immunodeficiency or immune dysregulation, which could lead to presentations with nonspecific systemic symptoms mimicking severe infections or sepsis. The acute presentation in this case highlights the importance of maintaining a high index of suspicion for lymphoid malignancies, including LD-CHL, particularly in elderly or immunocompromised patients by early histopathologic evaluation and prompt oncologic referral for accurate diagnosis and timely management.

EA4HP26-LYWS-24

Adult T-cell leukemia/lymphoma with HTLV-1-infected HRS-like cells (ATLL-HH)

Dr. Kennosuke Karube¹, Dr. Takeshi Okatani², Dr. Tsuyoshi Muta²

¹ Graduate School of Medicine, Nagoya University, Department of Pathology and Laboratory Medicine, Nagoya, Japan; ² Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Department of Hematology, Hiroshima, Japan

Case Description

A 81-year old male presented with cervical lymphadenopathy and shoulder pain. Positron emission tomography with Computed tomography (PET-CT) identified generalized lymphadenopathy with extranodal involvement of the bone and the spleen.

Blood test showed an elevated soluble IL-2 receptor and immunoglobulin. Anti-human T-lymphotropic virus type 1 (HTLV-1) antibody was positive. With the initial diagnosis of CHL, the patient received A+AVD therapy and Brentximab vedotin monotherapy. Metabolic CR was achieved and in CR status after 7 months of diagnosis.

Laboratory data at the diagnosis:

WBC 9000/ml (no atypical cells, eosinophils 2.0%), Hb 11.0 g/dl, Plt 49.6x10⁴/ml, LD 158 U/l, sIL2R 2392 U/ml (normal range, 157-474), TP 8.3 g/dl, Alb 2.7 g/dl, IgG 2791 mg/dl (861-1747), IgA 856 mg/dl (93-393), IgM 119 mg/dl (33-183), CRP 10.93 mg/dl, Anti-HTLV-1 antibody (+)(172.3 (<1.0))

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The normal lymph node architecture was completely effaced by infiltration of Hodgkin/Reed–Sternberg (HRS)–like giant cells admixed with numerous inflammatory cells, including eosinophils, lymphocytes, and histiocytes, imparting a “Hodgkin-like” appearance. No nodular sclerosis pattern was identified.

Immunophenotype

The HRS-like cells were positive for CD30, CD15, PD-L1, CD25, and pSTAT6, but negative for CD20, PAX5, Oct2, BOB1, CD3, CD4, CD5, CD7, CD8, TIA1, Granzyme B, CCR4, and EBER-ISH.

A small number of PD1-, TIA1-, Granzyme B-, and/or FOXP3-positive lymphocytes were scattered in the background.

RNA in situ hybridization for HTLV-1 basic leucine zipper factor (HBZ-ISH) demonstrated HTLV-1 infection in the HRS-like cells, whereas almost all background lymphocytes were negative.

Cytogenetics

Not done

Molecular Studies

No clonal T-cell receptor gamma (TCRG) gene rearrangement was detected by PCR using the BIOMED-2 protocol.

Proposed Diagnosis

Adult T-cell leukemia/lymphoma with HTLV-1 infected HRS-like cells (ATLL-HH)

Interesting Feature(s)

Adult T-cell leukemia/lymphoma (ATLL) is a T-cell neoplasm associated with human T-lymphotropic virus type 1 (HTLV-1). Involved lymph nodes in ATLL typically show diffuse proliferation of medium- to large-sized lymphoid cells with marked pleomorphism. However, several rare morphological variants have been reported, mimicking

anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, or exhibiting Hodgkin-like morphology, as in the present case.

The Hodgkin-like variant can be further divided into two patterns: Hodgkin-like ATLL and ATLL-HH. HTLV-1 infection mainly involves the medium-sized lymphoid cells surrounding the HRS-like cells in Hodgkin-like ATLL, whereas it is detected in the HRS-like cells themselves in ATLL-HH.

Further accumulation of similar cases is needed to clarify the pathogenesis including lineage distinction of HRS-like cells and the clinical impact of this rare morphological pattern.

Panel Diagnosis: Adult T-cell leukemia/lymphoma with Hodgkin like cells

EA4HP26-LYWS-28

EBV positive classic Hodgkin lymphoma with cytotoxic molecule expression and a concurrent small T-cell clone of uncertain significance

Dr. Vandana Panakka^{1,2}, Dr. Sara Monaghan^{1,2}, Dr. Katelynn Davis^{1,2}, Dr. Majd Jawad^{1,2}

¹ University of Pittsburgh, School of Medicine, Pittsburgh, USA; ² University of Pittsburgh Medical Center (UPMC), Department of Pathology, Division of Hematopathology, Pittsburgh, USA

Case Description

A 64-year-old female with past medical history of osteoarthritis, diverticulitis, and iron deficiency presented with two-months of fatigue, night sweats, poor appetite, weight loss, and mild abdominal pain. CT scans revealed bulky conglomerate mediastinal and retroperitoneal lymphadenopathy and a 5.0 cm right paravertebral mass. Laboratory studies showed microcytic anemia (Hb-5.6 g/dL, MCV 62 fL), mildly elevated white blood cell count (WBC 12.8 x 10⁹/L) with neutrophilia and a normal lymphocytic count.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

A biopsy of the paravertebral mass demonstrated scattered large cells in a background of small lymphocytes and occasional eosinophils. The large cells displayed bilobate or multilobate nuclei and a moderate amount of eosinophilic cytoplasm with a subset showing prominent nucleoli. They were morphologically compatible with Hodgkin and Reed Sternberg cells (H/RS cells).

Immunophenotype

The H/RS cells are positive for CD30, MUM1 and EBER with a subset positive for CD15. PAX5 is very weak and occasionally negative. The H/RS cells are positive for cytotoxic markers TIA and granzyme B, and negative for other T-cell markers including CD3, CD2, CD4, CD5, CD7, CD8, CD43 and ALK. Flow cytometric studies demonstrated a small atypical T cell population (2% of the total events) that is positive for CD4, CD56 and CD16/CD57 with loss of CD7 and mildly positively skewed TRBC1 expression. The CD4:CD8 ratio is normal, and B cells are polytypic by flow cytometry. Subsequent peripheral blood flow cytometry showed an atypical T cell population with a similar immunophenotype (4% of the total events).

Cytogenetics

N/A

Molecular Studies Molecular clonality studies for B-cell receptor by PCR (BIOMED-2) demonstrated clonal peaks: IgH (VDJ) FR2: Accentuated peak (264bp), IgH (VDJ) FR3: Clonal (123bp), IgK-VJ: Atypical peak (197bp), IgK-DE:

Clonal (372bp). T-cell receptor studies also demonstrated a clonal peak (TCRG 2.0: Clonal, 190bp) in a polyclonal background.

Proposed Diagnosis

Classic Hodgkin lymphoma, EBV positive, with cytotoxic molecule expression.

Interesting Feature(s)

We present a case of EBV positive CHL with cytotoxic molecule expression. PAX5 is a critical marker to confirm the B-cell nature of CHL. Our case shows characteristic CHL features; however, the very weak to absent PAX5 in H/RS cells, and the positive cytotoxic molecules (TIA-1, granzyme B), makes it challenging to distinguish CHL from ALK-negative anaplastic large cell lymphoma or other T-cell lymphomas. The EBV reactivity in the large abnormal cells steers us away from anaplastic large cell lymphoma, and all T-cell markers are negative in the abnormal cells in our case; however, T-cell lymphomas often show downregulation of T-cell markers. Indeed, studies have demonstrated frequently diminished or absent PAX5 in CHL with cytotoxic markers, which generally makes distinction from T-cell lymphomas a conundrum and prompts molecular testing. Thus, another challenging aspect of this case is the presence of a small, atypical T cell population by flow cytometry, identified in the tissue biopsy and a concurrent peripheral blood specimen. Since the addition of TRBC1 antibody to our T-cell flow cytometry panel, we frequently identify small T-cell clones of uncertain significance in healthy individuals and in the context of other neoplastic proliferations. These small T-cell clones usually lead to positive T-cell clonality studies by PCR, as seen in our case, adding to the complexity of the evaluation.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-positive) with unusual phenotype (expression of all cytotoxic molecules)

EA4HP26-LYWS-41

Classical Hodgkin lymphoma, mixed cellularity type with expression of cytotoxic granules.

Dr. Gorana Gasljevic^{1,4}, PhD/MD student Panna Dora¹, PhD/MD Ira Kokovic², Prof. Alexandar Tzankov³

¹ Institute of Oncology Ljubljana, Department of Pathology, Ljubljana, Slovenia; ² Institute of Oncology Ljubljana, Department for Molecular Diagnostics, Ljubljana, Slovenia; ³ Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland; ⁴ Faculty of Medicine, University of Maribor, Maribor, Slovenia

Case Description

Case dating to 2011. 58-yrs old male, otherwise healthy. He reported slowly enlarging lymph nodes on the left aspect of his neck lasting for 5 yrs but starting to increase substantially only recently. He denied B symptoms. Physical examination showed left neck lymphadenopathy up to 3 cm. At the time of submission L 7.4 x 10⁹/L, Hb 135 g/L, Plt 321x10⁹, LDH 2.11 ukat/L (norm<4.2 ukat/L), CRP 41. PET CT: increased uptake with SUV up to 10 in numerous lymph nodes on the left side of the neck, the largest one measuring 4 cm with no other foci of increased uptake elsewhere in the body. Bone marrow biopsy and aspirate were negative for lymphoma infiltration. Primary clinical stage was IA. He was treated with 3 cycles chemotherapy according to ABVD protocol and radiotherapy with 30,6 Gy in 17 fractions on the left side of the neck. He has been checked by regular clinical controls from the beginning of 2012 when treatment was completed until the end of 2015; in that period there was no recurrence. After 2015 he was lost for follow up.

Biopsy Fixation Details

10% buffered formalin overnight

Frozen Tissue Available

No

Details of Microscopic Findings

Diffusely effaced LN architecture. Diffuse infiltration by epithelioid histiocytes giving Lennert lymphoma-like appearance. In between there are many small reactive lymphocytes, plasma cells, eosinophils, and large atypical mononuclear, binuclear and multinuclear cells with large, vesicular nuclei, pronounced eosinophilic nucleoli and copious cytoplasm (RS and H-cells). Many mummified cells are present.

Immunophenotype

Large atypical cells are positive for CD30, CD15, PAX-5, MUM-1, EMA, Perforin, TIA-1, PD-L1, pSTAT5B and negative for CD3, CD4, CD5, CD8, LCA, Granzyme B, OCT2, BOB1, EBV-ISH, pSTAT3, STAT6, TCRB,TCRG.

Cytogenetics

NA

Molecular Studies

PCR Biomed-2 polyclonal B and polyclonal T (IgH FR1-3 & IgK-A,IgK-B; TCRB, TCRG).

Proposed Diagnosis

Classical Hodgkin lymphoma, mixed cellularity type with expression of cytotoxic granules.

Interesting Feature(s)

Slowly developing disease in the course of 5 yrs with limited stage IA and no recurrences after only three cycles of chemotherapy and radiotherapy together with polyclonal B and T patterns by PCR, PDL1 and pSTAT5 expression and absence of pSTAT3 expression are in favor of cHL with cytotoxic granule expression. ALK- ALCL could rarely be positive for CD15 and PAX5 and could express PDL1 which is regulated by STAT3 and MYC. EMA and cytotoxic granules expression points in the favor of ALK- ALCL diagnosis but no PCR analysis and pSTAT5 positive reaction while pSTAT3 is negative. Diagnosis of cHL-like ALK-ALCL seems to be less likely. Case nicely illustrates necessity of additional testing in this rare variant of cHL.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-positive) with unusual phenotype

EA4HP26-LYWS-47

CD30 negative classic Hodgkin lymphoma with granulomatous background in a patient with history of marginal zone lymphoma

Dr. Jiehao Zhou

Mayo Clinic Arizona, Lab Med and Pathology, Phoenix, USA

Case Description

This a a 55-year-old female with a history of marginal zone lymphoma status post radiation therapy and Rituximab approximately 4 years ago. She presented with B symptoms and tracer avid cervical, axillary, subpectoral, mediastinal, right internal mammary, abdominopelvic, and inguinal lymph nodes on PET/CT. Previous excisional biopsy of a left axilla lymph node was performed at an outside institute and reported as "reactive with collection of epithelioid histiocytes". The diagnostic material of pervious biopsy was unavailable for evaluation.

The patient's CBC are essentially unremarkable at the current presentation: WBC 8.7 k/cumm, Hgb 12.7 gm/dL, MCV 90.4fl, Platelet 312 k/cumm.

Excisional biopsy of right groin lymph node (current case) is performed. Flow cytometric analysis shows no abnormal lymphoid population.

Biopsy Fixation Details

Fixed in 10% neutral buffered formalin for overnight.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Effacement of architecture by an abnormal infiltrate with a heterogeneous mixture of cells and granulomatous inflammation. The infiltrate contains many histiocytes, including multinucleated giant cells, plasma cells, small lymphocytes and eosinophils. In addition, there are scattered large abnormal multilobated nuclei and prominent eosinophilic nucleoli. Occasional mummified large abnormal cells are seen.

Immunophenotype

CD20: Positive small B-cells. Large abnormal cells negative.

CD19: Similar to CD20; large abnormal cells negative.

Pax-5: Strong staining with distribution similar to CD20 and weak staining of large abnormal cells.

CD79a: Staining of small lymphoid cells and plasma cells; large abnormal cells negative.

CD3: Moderate number of positive lymphoid cells; large abnormal cells negative.

CD30: A few scattered positive transformed lymphoid cells. Most large abnormal cells negative.

CD15: Staining of granulocytes and some large abnormal cells.

OCT2: Staining of small lymphoid cells; large abnormal cells negative.

BOB 1: A few positive cells, including staining of occasional large abnormal cells.

MUM-1: Large abnormal cells positive.

BCL6: A moderate number of scattered positive cells. Possible staining of rare large abnormal cells.

CD43: Staining of histiocytes and some lymphoid cells; large abnormal cells appear negative.

CD45: Staining of histiocytes and small lymphoid cells. Large abnormal cells difficult to interpret, but appear negative.

Cyclin D1: Staining of some histiocytic/dendritic cells; large abnormal cells negative.

ALK1: Negative.

CD68: Highlights histiocytes. Most large abnormal cells negative.

CD138: Moderate number of positive plasma cells; large abnormal cells negative.

Kappa in Situ: A few scattered positive plasma cells.

Lambda in Situ: A few scattered positive plasma cells.

EBV (EBER) in Situ: Negative.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Classic Hodgkin lymphoma, CD30 negative with a granulomatous background

Interesting Feature(s)

- CD30 negative classic Hodgkin lymphoma, very rare
- Granulomatous reaction, which can be occasionally seen in CHL, can sometimes mask the presence of lymphoma, leading to potential misdiagnosis or delayed treatment.
- History of marginal zone lymphoma, raising a possibility of transformation from a preexisting low grade B cell lymphoma. There is no evidence of marginal zone lymphoma in the current case. Due to lack of diagnostic material of MZL, a comparison study cannot be performed

Panel Diagnosis: Classic Hodgkin lymphoma (EBV-negative) with unusual immunophenotype (CD30 negative) and granulomatous inflammation

Classical Hodgkin's lymphoma with marked granulomatous reaction mimicking sarcoidosis

Dr. Rosa Brand, Dr. Ingrid Simonitsch-Klupp

Medical University of Vienna, Dep. of Pathology, Vienna, Austria

Case Description

73 year old woman with a history of Axillary lymphadenopathy (01/2025, 07/2025) with lymph node exstirpations at an external institute;

- Original diagnosis (2x): sarcoidosis; treatment with corticosteroids, MTX, Puri-Nethol; à no improvement;
- Weight loss (>10% TBW), night sweats;

progressive advanced lymphadenopathy (axillary, supraclavicular, paraaortal, retroperitoneal conglomerates), splenomegaly, FDG PET-CT + (Deauville Score 5)

- Re-evaluation of lymph-node-histology at our institution, correction of diagnosis;
- Prior diseases:
 - Peripheral pulmonary embolism, left lower lobe (09/2025)
 - Right renal cell carcinoma, partial nephrectomy (04/2025)
 - Seronegative rheumatoid arthritis with sicca symptoms
 - Erythema nodosum of the right lower leg following influenza and COVID infection
 - Neuroborreliosis with left-sided facial nerve palsy (10/2021)

Biopsy Fixation Details

10% buffered formaline

Frozen Tissue Available

no

Details of Microscopic Findings

Histology of both excised lymph nodes:

Nodal architecture effaced by numerous, partly confluent epithelioid granulomas without necrosis; occasionally multinucleated giant cells (Langhans-type) within granulomas; overall a sarcoid-like granulomatous appearance

- background of small lymphocytes, histiocytes, plasma cells and very rare eosinophilic granulocytes
- high power: few classical Hodgkin (H)- and Reed-Sternberg (RS) cells admixed

Immunophenotype

H- and RS-cells:

CD30+, CD15+, PAX-5+ (weak), MUM-1+, CD79a+/- (weak), IMP3+; LMP-1-, EBER-ISH-, CD20-, CD3-

Background:

epithelioid histiocytes: CD68R+, PD-L1++, CD163-+

lymphocytes: CD3+ T cells and CD20+ B cells

Cytogenetics

not done

Molecular Studies

not done

Proposed Diagnosis

Classical Hodgkin's Lymphoma (mixed cellularity), EBV-, with marked granulomatous reaction simulating sarcoidosis.

Interesting Feature(s)

- Extensive granulomas obscuring the presence of neoplastic H-RS cells, hence originally misdiagnosed as sarcoidosis; delayed diagnosis of cHL (MC) on review.
- Although slight granulomatous reaction is a common feature of MC cHL, the

extent in this case (>90%) is very unusual.

- The presence of extra-thoracic lymphadenopathy, which points to sarcoidosis, may be indicative of lymphoma with a granulomatous reaction. Lymphoma should therefore be ruled out with IHC.
- Pronounced expression of PD-L1 on H-RS cells and on epithelioid histiocytes points to immune escape mechanisms.
- Patient has a history of immunosuppression (RA), but cHL shows no association with EBV.

Panel Diagnosis: Classic Hodgkin Lymphoma with marked granulomatous reaction mimicking sarcoidosis

EA4HP26-LYWS-58

EBV-positive lymphocyte-rich classic Hodgkin lymphoma

Dr. Samuel J. Wu, Dr. Rebecca L. King

Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, USA

Case Description

A 50-year-old male presented with left axillary lymphadenopathy. Clinical history is significant for classic Hodgkin lymphoma (CHL) four years prior, with complete remission after six cycles of Adriamycin-bleomycin-vinblastine-dacarbazine (ABVD) (pathology not reviewed at our institution). FDG-PET now shows a 2.9 cm lymph node with avidity. Core needle biopsy showed an atypical lymphoid infiltrate with scattered EBV-positive cells. Excisional biopsy was performed for definitive diagnosis.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not applicable.

Details of Microscopic Findings

The lymph node shows architectural effacement with regressed germinal centers surrounded by expanded and serpiginous mantle zones and without nodular sclerosis or fibrosis. Within the interfollicular areas are singly scattered large, atypical cells with irregular nuclei, vesicular chromatin, prominent nucleoli, and occasional binucleation, compatible with Hodgkin Reed-Sternberg (HRS) cells. The background is composed of small lymphocytes and epithelioid histiocytes without eosinophils or significant spectrum of plasma cells and immunoblasts.

Immunophenotype

The HRS cells are positive for CD15, CD30, OCT2, PAX5 (weak), and EBER-ISH, and are negative for CD20, CD45, and MEF2B. No obvious rosetting is seen with CD279 (PD1) or CD3. IgD positive small B cells are located in mantle zones but are not prominent in the areas of the HRS cells. In focal areas, EBER also shows positivity in a population of small B-cells.

Cytogenetics

Not evaluated.

Molecular Studies

Not evaluated.

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-rich subtype with background EBV reactivation of uncertain significance.

Interesting Feature(s)

The morphologic findings of this case highlight the potential overlap between lymphocyte-rich CHL (LR-CHL) and nodular lymphocyte predominant B-cell lymphoma/Hodgkin lymphoma (NLPBL/NLPHL), while the immunophenotypic findings and subtle microenvironment pattern demonstrate the key distinguishing features between the two entities. In this case the uniform and strong expression of CD30 and CD15, dim PAX5 and lack of

CD45, CD20, and MEF2B support the diagnosis of CHL rather than NLP. As seen in this case, OCT2 positivity in CHL can occur (especially in LR-CHL), highlighting a potential diagnostic pitfall. EBER positivity also favors CHL, although a subset of NLP cases can be positive. EBV-positivity is less common in LR-CHL than other subtypes, with reports generally ranging from 10-30% of cases. LR-CHL features small, regressed background germinal centers, often with expanded mantle zones, in contrast to NLP in which the mantle zones expand around the LP cells creating the macrofollicle architecture (and highlighting the germinal center derivation of the LP cells). The HRS cells in this case are in an interfollicular distribution within a T cell-rich microenvironment.

A second interesting feature of this case is the presence of small EBER positive B cells in addition to the HRS cells, which challenges the canon that EBER should only be found in the HRS cells in CHL. Nevertheless, we were confident in the other morphologic and phenotypic features of the case and do not believe this to represent a polymorphic EBV-positive lymphoproliferation. While speculative, we attributed the EBER positivity in small B cells to local EBV-reactivation.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-positive) with EBV lymphoproliferation in the background

EA4HP26-LYWS-59

Classic Hodgkin Lymphoma, “essentially” CD30 (BerH2) negative

Dr. Parastou Tizro, **Dr. Lori Soma**, Dr. Joo Song, Dr. Raju Pillai, Dr. Karl Gaal, Dr. Young Kim, Dr. Olga Danilova, Dr. Michelle Afkhami, PhD/MD Winston Lee

City of Hope Medical Center, Pathology, Duarte, USA

Case Description

44 year old female with bulky mediastinal disease and night sweats.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

n/a

Details of Microscopic Findings

Fibrosclerotic tissue with nodular lymphoid proliferation, including scattered large atypical binucleate and mononuclear cells (vesicular chromatin, prominent nucleoli), and some mummified cells. Associated scattered histiocytes with a few eosinophils and plasma cells.

Immunophenotype

- o Positive: CD15, PAX5 (weak), FASCIN, TARC, MUM1, GATA3, PDL1
 - Focal, minimal CD30 (Ber-H2). Similar results when performed on other blocks and at two outside laboratories.
 - More significant but still subset expression of CD30 using Cell Signaling antibody (CST rabbit monoclonal/ E4L4I)
- o Negative: CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD45, CD56, CD79A, CD123, CD138, EBER, OSCAR, S100, SOX10, OCT2, BOB1, TIA1, Perforin, ALK, Granzyme B, kappa, lambda

Cytogenetics

n/a

Molecular Studies

- o TCR sequencing: negative
- o B cell clonality (PCR): IGH and IGK clones detected
- o NGS: *B2M* p.R3Pfs*5 (4% VAF), *BTG1* p.Y67* (3% VAF), *GNA13* p.D182Efs*29 (3% VAF), *SOCS1* p.H90Rfs*22 (4% VAF), *TNFAIP3* p.E132* (3% VAF). Amplification of *HRAS*, *IGF2*, *PDCD1*

Proposed Diagnosis

Classic Hodgkin Lymphoma, Nodular Sclerosis type

Interesting Feature(s)

- CD30 BerH2 IHC is mostly negative, with more significant expression using CD30 research clone (CST rabbit monoclonal/ E4L4I).
- Thymus and Activation-Regulated Chemokine (TARC) IHC can be helpful in challenging diagnoses.

Follow-up: The patient received AVD+Nivolumab. The patient has responded to therapy, with the most recent PET CT showing decreased size and activity; however, persistent focus of increased uptake.

Peh SC, Kim LH, Poppema S. TARC, a CC chemokine, is frequently expressed in classic Hodgkin's lymphoma but not in NLP Hodgkin's lymphoma, T-cell-rich B-cell lymphoma, and most cases of anaplastic large cell lymphoma. Am J Surg Pathol. 2001 Jul;25(7):925-9. doi: 10.1097/00000478-200107000-00011. PMID: 11420464.

Veldman C, Rosati S, van den Berg A, et al. TARC Immunohistochemistry in the diagnosis of Classical Hodgkin Lymphoma. Hemasphere. 2018 Oct 30;2(Suppl 3):7. doi: 10.1097/01.HS9.0000547859.97007.b3. PMCID: PMC8925828.

Panel Diagnosis: Classic Hodgkin lymphoma (EBV-negative) with unusual immunophenotype (CD30 essentially negative)

EA4HP26-LYWS-65

Classical Hodgkin lymphoma with an unusual blast-rich growth pattern

Dr. Maysaa Abdulla

Region Uppsala, Clinical pathology, Uppsala, Sweden

Case Description

A 75-year-old man previously healthy, presented with a left axillary lymphadenopathy. No B-symptoms. No organomegaly.

Biopsy Fixation Details

The lymph node specimen measuring 22 mmX18 mm was fixed in buffered 4% formalin.

Frozen Tissue Available

No frozen tissue available

Details of Microscopic Findings

An enlarged lymph node with effaced architecture and extensive sinusoidal infiltration by large mononuclear tumor cells with prominent nucleoli; occasional multinucleated tumor cells were noted.

Immunophenotype

The tumor cells show positive protein expression of CD30, MUM1, PAX5 with variable intensity, and partial expression of CCL17. There was no positive protein expression of CD45, CD20, CD79a, CD19, CD3, CD4, CD15, ALK, EBER.

Cytogenetics

Not done

Molecular Studies

Molecular analysis show polyclonal T-cell population and polyclonal B-cell population, however the findings are difficult to interpret due to low DNA quality.

Proposed Diagnosis

Lymph node with involvement by CD30+ lymphoma, with an immunophenotype most consistent with classical Hodgkin lymphoma, but with an unusual blast-rich growth pattern.

Interesting Feature(s)

The morphological findings are more consistent with CD30+ large Cell lymphoma, but the immunophenotype is most consistent with classical Hodgkin lymphoma.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV negative) mixed cellularity

EA4HP26-LYWS-67

High-risk lymphocyte-rich classic Hodgkin lymphoma presenting in a young man

Dr. Justin Kelley

Vanderbilt University Medical Center, Department of Pathology, Microbiology and Immunology, Nashville, USA

Case Description

17 year old man presented with significant weight loss (110 pounds over nine months) and vomiting in the setting of a small bowel obstruction. Workup was remarkable for bulky right cervical, mediastinal, perihilar and right inguinal lymphadenopathy. He was staged IIIB and received five cycles of Bv-AVE-PC (vincristine mostly held due to history of bowel obstruction/ileus) with remission. He remains well about 1.5 years after therapy with routine clinical evaluation every 3 months.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Sections of a right cervical lymph node show an enlarged lymph node effaced by a diffuse lymphohistiocytic infiltrate. Scattered throughout the small lymphocytes and histiocytes are many large, atypical HRS-like cells. No significant polymorphous inflammation including granulocytes is seen.

Immunophenotype

The large, atypical cells are positive for PAX5 (weak), CD30 (strong) and CD15 (subset). The cells are negative for CD20, CD45 and EBER ISH. CD21 shows focal small meshworks. CD3 highlights background T cells including focal T-cell rosettes around the large cells. Flow cytometry showed polytypic B cells and CD8-skewed T cells (CD4:CD8 = 0.4).

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-rich

Interesting Feature(s)

Lymphocyte-rich classic Hodgkin lymphoma is a rare lymphoma, even among classic Hodgkin lymphoma. It more frequently presents as low stage (stages I-II) disease in peripheral lymph nodes of middle-aged men with infrequent B-type symptoms and mediastinal involvement. These typical clinical features are virtually opposite in this young patient who presented with high stage disease with marked B-type symptoms and bulky, including mediastinal, lymphadenopathy. EBV, which is more common in lymphocyte-rich subtype, was also negative in this case. Fortunately, he responded well to therapy and remains in remission with close clinical follow up.

Panel Diagnosis: Classic Hodgkin lymphoma (no subtype possible on slide)

Mediastinal grey zone lymphoma: A microenvironment-rich tumor and a diagnostic challenge

Dr. Chuan Chen¹, Dr. Adam J. Wood¹, Dr. Dragan Jevremovic¹, Dr. Mike S. Bold², Dr. Ellen D. McPhail¹, Dr. Eric D. Hsi¹, Dr. Rebecca L. King¹

¹ Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, USA; ² Mayo Clinic, Department of Radiology, Rochester, USA

Case Description

A 21-year-old female presented with widespread pruritus for three months, followed by constitutional symptoms. PET-CT scan showed a large mediastinal mass and FDG-avid lymphadenopathy above and below the diaphragm, along with splenic masses and abnormal uptake in the pleura and pericardium. Core needle biopsy of the left cervical lymph node (LN) showed an unclassifiable large B-cell lineage lymphoma with CD30 expression and excision was recommended. Left axillary LN excisional biopsy was performed. The patient received dose-adjusted R-EPOCH, followed by BV-ICE salvage, and achieved a complete metabolic response. She is currently being evaluated as a candidate for autologous stem cell transplantation.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections of the lymph node show effaced nodal architecture by an atypical lymphohistiocytic infiltrate in a background of fine fibrosis. There is a population of large neoplastic cells with centroblastic morphology and clear cytoplasm, with some forms showing more lobulated nuclei. In some areas, these form sheets; however, in other areas, the large neoplastic cells are less dense and associated with pockets of eosinophils. Histiocytes are admixed throughout.

Immunophenotype

CD20 is strong and uniform on a subset of the tumor cells but varies, with a significant subset being completely negative. PAX5 is strong and uniform while other pan-B cell markers are lost to varying degrees with partial weak CD79a, very weak/partial OCT2, and loss of CD19, CD22, and BOB1. Tumor cells are negative for CD45 and express CD30 (partial with varying degrees of intensity), and with rare cells positive for CD15. Additional positive markers include BCL2 (partial), MUM1, and MYC (partial). They do not stain for kappa or lambda and are negative for CD10, BCL6, MEF2B, and EBER. CD3 stains abundant background T-cells.

Cytogenetics

FISH showed a *MYC* rearrangement in 31% of nuclei. No fusion of *MYC* and *IGH* and no rearrangement of *BCL2* or *BCL6* was seen.

Molecular Studies

Lymph3Cx: PMBL-like gene expression signature

Proposed Diagnosis

Mediastinal grey zone lymphoma

Interesting Feature(s)

Mediastinal grey zone lymphoma (MGZL) is an aggressive B-cell lymphoma with a histiocyte-rich background. This case represents a diagnostic challenge with a differential diagnosis of primary mediastinal large B-cell lymphoma (PMBL), classic Hodgkin lymphoma (CHL), and MGZL. In some areas, the tumor cells exhibit a diffuse growth pattern, while in other areas, they are loosely aggregated in a polymorphous inflammatory background. However, there is a spectrum from one to another, rather than two distinct morphologies to suggest a composite lymphoma. The cells

are more in keeping with PMBL than CHL cytologically, with some pleomorphism. With sheet-like growth and CD20 expression, PMBL was considered. However, the significant loss of the B-cell program, along with loss of CD20 in some areas, and loss of CD45 altogether preclude that diagnosis. CD30 expression and CHL-like morphology can be found; however, the CD30 is variable, and the sheet-like growth with strong CD20 expression in other areas argue against this diagnosis.

This case also highlights that MGZL patients can have widespread disease.

The diagnostic boundaries between MGZL and PMBL or CHL remain difficult to define in light of the biological spectrum. A core needle biopsy may capture only partial features; therefore, the diagnosis of MGZL should be made on excisional biopsy specimens.

Panel Diagnosis: Classic Hodgkin Lymphoma rich in tumoral cell with partial intense expression of CD20 and sheet of large cells but loss of other B cell markers

EA4HP26-LYWS-87

Composite classic Hodgkin lymphoma and Rosai-Dorfman disease

PhD/MD Pedro Farinha^{1,2}

¹ BC Cancer, Pathology, Vancouver, Canada; ² UBC, Lab Med, Vancouver, Canada

Case Description

72-year-old woman with a history of multiply relapsed marginal zone lymphoma since September 1999. She has rituximab-induced hypogammaglobulinemia and receives monthly IVIG infusions.

In February 2024, she developed B symptoms, following travel to Mexico, with positive Dengue serology IgG+. Subsequent CT imaging demonstrated multiple osseous lesions and an L4/L5 paraspinal mass; biopsy at that time was non-diagnostic. A PET scan in June 2024 showed limited abdominopelvic lymphadenopathy (largest node 1.9 cm, SUV 5.6) and multiple hypermetabolic osseous lesions (SUV max 18 in the sacrum).

Two biopsies were then performed: Left iliac bone (#1) on August 15, 2024; Bone marrow (#2) on October 4, 2024 (specimen submitted).

As of December 2025, the patient has completed LYBVA/DBV therapy (sequential BV followed by AVD). End-of-treatment CT imaging showed no new structural lesions; however, PET scan demonstrated focal metabolic progression, with small bone lesions (SUV max 7.3).

A recent BM biopsy (December 3, 2025; not reviewed) was negative for CHL but noted increased histiocytes.

Biopsy Fixation Details

B-plus

Frozen Tissue Available

No

Details of Microscopic Findings

Biopsy #1: Fragmented bone and marrow tissue cores show a polymorphic infiltrate composed of numerous histiocytes, many with abundant clear cytoplasm, ill-defined borders, and round nuclei with occasional prominent nucleoli. Focal emperipolesis is present. The histiocytes are admixed with small lymphocytes, scattered granulocytes, and rare plasma cells.

Biopsy #2: Some marrow spaces show a diffuse polymorphic infiltrate within a markedly fibrotic background, composed of numerous small lymphocytes and histiocytes with admixed eosinophils and plasma cells. Scattered large, atypical cells with monolobated and polylobated pleomorphic nuclei and prominent eosinophilic nucleoli are

present, consistent with Hodgkin/Reed-Sternberg (HRS) cells. Many histiocytes exhibit abundant clear cytoplasm with ill-defined borders and round nuclei with occasional nucleoli. Focal emperipolesis is noted.

Immunophenotype

Biopsy #1: The large histiocytes are positive for CD68, CD163 as well as strong S100 and significant cyclin D1. These cells are negative for CD1a and BRAFV600E immunostains. Significant atypical cells are not seen on CD1a, CD3, CD10, CD15, CD20, CD21, CD30, CD34, CD56, CD79a, CD117, PAX5, BCL6, MUM1, MYC, kappa, lambda, ALK, MPO, TP53, SOX10, cytokeratins and EBV EBER ISH. Biopsy #2: The large HRS cells co-express strong CD30, CD15 and MUM1 as well as dim PAX5. They are negative for CD3, CD20, CD45, CD79a and EBV EBER ISH. The abundant histiocytes show strong uniform staining for CD68, CD163, S100 and cyclin D1. The small lymphocytes are small CD3+ T cells.

Cytogenetics

Not done

Molecular Studies

Not done

Proposed Diagnosis

Composite classic Hodgkin lymphoma and Rosai-Dorfman disease

Interesting Feature(s)

Composite classic Hodgkin lymphoma (CHL) with Rosai-Dorfman disease (RDD) is rare.

This case also demonstrates an atypical presentation of CHL, characterized by predominantly extranodal and osseous involvement.

Although EBV-negative, the patient's rituximab-induced hypogammaglobulinemia may suggest an iatrogenic secondary immunodeficiency context.

In contrast to sporadic RDD, the molecular drivers of RDD arising in association with neoplasms remain undefined. The coexistence of CHL and RDD is more likely immunologic than genetic in nature, reflecting cytokine-mediated immune dysregulation induced by CHL and likely facilitated by the patient's secondary immunodeficiency.

Panel Diagnosis. Composite Classic Hodgkin Lymphoma and Rosai Dorfmann disease

EA4HP26-LYWS-89

CD30 negative classic Hodgkin lymphoma

Alma R. Oskarsdottir, Rebecca L. King, **Joanna C. Dalland**

Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, USA

Case Description

The patient is a 68-year-old man with past medical history significant for coronary artery disease, hypertension, chronic kidney disease and chronic hypoxemic respiratory failure who underwent evaluation for hypoxemia. He was found to have FDG avid (SUV max 15.8) right cervical lymphadenopathy, up to 5.9 cm, and patchy mild FDG uptake throughout both lungs, greatest along pleural surfaces. Fine needle aspiration and a core needle biopsy of a right cervical lymph node was performed. The biopsy showed focal non-caseating granulomas and workup was not diagnostic for involvement by lymphoma. A subsequent excisional biopsy of a right neck level III lymph node was performed (provided case).

Biopsy Fixation Details

Fixed in 10% neutral-buffered formalin for > 24 hours.

Frozen Tissue Available

None.

Details of Microscopic Findings

The lymph node architecture is effaced by an abnormal lymphohistiocytic infiltrate with a nodular growth pattern. The capsule is thickened, and the nodules are focally surrounded by thick bands of fibrosis.

The nodules contain scattered large, atypical cells with irregular nuclear contours, vesicular chromatin, large prominent nucleoli and abundant eosinophilic cytoplasm, consistent with Hodgkin/Reed-Sternberg (H/RS) cells.

The large cells are associated with a mixed inflammatory background containing small lymphocytes, plasma cells, histiocytes and occasional eosinophils. Focal clusters of epithelioid histiocytes are seen.

Immunophenotype

The H/RS cells are positive for CD15, MUM1 and PAX5 (weak). They are negative for CD30, CD20, CD45, OCT2, MEF2B, and EBV-ISH.

CD3 highlights numerous background small T-cells that form rosettes around the H/RS cells. There are background small CD20-positive B-cells within residual follicles. Background small B-cells and plasma cells are polytypic for kappa and lambda.

Cytogenetics

None.

Molecular Studies

None.

Proposed Diagnosis

Classic Hodgkin lymphoma, nodular sclerosis (WHO 5th)

Nodular sclerosis classic Hodgkin lymphoma (ICC 2022)

Interesting Feature(s)

CD30 is a transmembrane receptor from the tumor necrosis factor receptor superfamily. CD30 and CD15 are expressed in the vast majority of classic Hodgkin lymphoma (CHL) cases and show membranous staining pattern with accentuation of the Golgi system. CD15 is known to be negative in 15-25% of CHL.

Although CD30 is positive in almost all cases of CHL, rare CD30-negative CHL have been reported and pose a significant diagnostic challenge. To make the diagnosis of CHL in the setting of CD30 negativity, morphologic features and other immunophenotypic features must be consistent with the disease. It is important to consider and rule out other entities that can present with similar morphologic features and to rule out issues with tissue processing/antigen retrieval in the staining process. This can be done by evaluating internal controls and repeating the stain if indicated. In the provided case, CD30 highlighted background immunoblasts, indicating successful staining of the tissue.

In our case, the morphologic features are characteristic of CHL and extensive immunohistochemical panel performed is in keeping with the diagnosis. Importantly, other B-cell lymphomas that can show similar morphologic features, including nodular lymphocyte predominant Hodgkin lymphoma/B-cell lymphoma is ruled out with multiple germinal center B-cell markers.

The patient received AVD chemotherapy directed against CHL and achieved full remission with no evidence of disease recurrence to date.

Panel Diagnosis: Classic Hodgkin lymphoma (EBV-negative) with unusual immunophenotype (CD30 negative) nodular sclerosis

An unusual presentation of an unusual variant of classic Hodgkin lymphoma

Dr. Connor Hartzell¹, Dr. Megan C. Smith^{1,2}, **Dr. Emily F. Mason**¹

¹ Vanderbilt University Medical Center, Department of Pathology, Microbiology and Immunology, Nashville, USA; ² Summa Health, Akron, USA

Case Description

A 21-year-old female with a 10-year history of an untreated chronic skin rash on her left arm incidentally noted lymphadenopathy in her left elbow/upper arm. MRI showed 3 subcutaneous lesions; the largest was 3 cm in size, located 2 cm proximal to the medial joint line. An excisional lymph node biopsy was performed. Subsequent PET scan showed multiple faintly to mildly FDG avid lymph nodes in the left elbow, measuring up to 1.3 cm/max SUV 3.6; and multiple faintly to mildly FDG avid bilateral inguinal lymph nodes, including a 1.3 cm/max SUV 3.7 right inguinal node. There was no evidence of lymphadenopathy in the neck, chest, or axilla. The patient had no other significant history and, other than some fatigue, had no symptoms.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

H&E-stained sections showed an enlarged lymph node partially involved by a vaguely nodular atypical lymphoid infiltrate with scattered variably regressed germinal centers. Within the vaguely nodular areas were scattered large abnormal cells with round to irregular to occasionally multilobated nuclei, vesicular chromatin, prominent nucleoli, and abundant cytoplasm. The background infiltrate consisted predominantly of small lymphocytes. There were no granulomata, areas of necrosis, or banding fibrosis. Uninvolved areas at the periphery of the node showed reactive-appearing germinal centers.

Immunophenotype

Immunohistochemical stains showed that the vaguely nodular areas contained serpiginous nodules composed predominantly of small CD20+ B cells, with associated regressed germinal centers. The large abnormal cells were admixed within the B cell nodules and were positive for PAX5 (weak), CD30, CD15 (subset), and MUM1 (weak) and negative for CD20, CD19, CD79a, BCL6, OCT2, and CD3. There was rimming of the large abnormal cells by CD3+, PD-1+ T cells. EBER in situ hybridization was negative. A CD21 stain highlighted follicular dendritic cell meshworks underlying the regressed germinal centers. Flow cytometry showed polytypic B cells and normal T cell subsets.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Lymphocyte-rich classic Hodgkin lymphoma

Interesting Feature(s)

Several features made this case diagnostically challenging, including the relative rarity of the lymphocyte-rich (LR) variant of classic Hodgkin lymphoma (CHL). However, the lesional cells showed an immunophenotype typical of Reed-Sternberg cells, and the architecture of the lesion was most in keeping with LR-CHL. The distribution of disease – predominantly in the upper arm, with possible inguinal lymph node involvement, with lack of disease in the chest, neck, or axilla – was unusual for CHL. Additionally, the history of a chronic skin rash in the area of the biopsied lymph node raised the question of whether the lymphadenopathy could be reactive in nature. The histology of the lesion favored a neoplastic process; however, the patient's history did raise the question of whether chronic immune

activation may have contributed to lymphomagenesis in this case. Finally, the clinician noted that the relatively low level of PET avidity (SUV 3.6) was unusual for CHL. However, given the epidemiology of CHL, clinical experience and published studies are likely biased toward nodular sclerosis CHL. Given disease histology, one might expect LR-CHL to show levels of PET avidity more similar to nodular lymphocyte predominant Hodgkin/B-cell lymphoma, which has been reported to show lower SUV levels than CHL. The patient received 2 cycles of ABVD followed by radiation. An end of therapy PET scan showed an excellent response to treatment.

Panel Diagnosis: Lymphocyte-Rich Classic Hodgkin Lymphoma with untypical clinical presentation

EA4HP26-LYWS-97

Classic Hodgkin Lymphoma, CD30-negative

Prof. Siok-Bian Ng¹

¹ National University of Singapore, Yong Loo Lin School of Medicine, department of Pathology, Singapore, Singapore; ² National University Hospital, Department of Pathology, Singapore, Singapore

Case Description

36-year-old Malay man presented with persistent cough for 3 months and B symptoms in Nov 2024. He has history of diabetes and hyperlipidaemia. PET scan revealed bilateral supraclavicular FDG-avid adenopathy and bulky mediastinal mass. Hepatitis B, Hepatitis C and HIV are negative. Left lower cervical LN biopsy was performed and he was diagnosed with early unfavourable Hodgkin lymphoma, stage IIB with bulky disease. Patient received 2 cycles of ABVD and 4 cycles of AVD. Interval PET in Aug 2025 revealed complete metabolic response.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

Nil

Details of Microscopic Findings

The lymph node architecture was effaced by a nodular and heterogeneous population of inflammatory cells with large areas of necrosis within the nodules. The capsule is fibrotic and thickened. The nodules contain a mixture of small lymphocytes, histiocytes, plasma cells and eosinophils. Within this reactive inflammatory background are scattered and large aggregates of large Hodgkin/Reed-Sternberg (HRS) cells with multi-lobated nuclei and prominent eosinophilic nucleoli. Lacunar cells, mummified cells and smaller monolobated cells are also evident. The central necrosis is associated with acute inflammation and foamy macrophages.

Immunophenotype

- The large HRS cells are mostly negative for CD30. CD30/PAX5 double stain shows the scattered CD30+ cells are negative for PAX5. HRS cells are positive for CD15 (strong), PAX5 (weak), MUM1 and GATA3. Rare HRS cells express CD79A.
- HRS cells do not express CD20, OCT2, BOB1, LCA, ALK1, granzyme B, TIA1 and T-cell markers (TCRG, TCRB, CD2, CD5, CD7 and CD3).
- The background small lymphocytes are predominantly CD3+ T cells with fewer CD20+ B cells.
- EBER in situ hybridisation is negative.

Cytogenetics

Nil

Molecular Studies

Flow cytometry showed No evidence of lymphoma. T cells make up 82.9% of the lymphocytes and show unremarkable phenotype with polytypic distribution of TCR α 1 and TCR α 2.

Clonality study: IgH: Monoclonal rearrangement, IgK: Monoclonal rearrangement

Proposed Diagnosis

Classic Hodgkin Lymphoma, nodular sclerosis, CD30-negative

Interesting Feature(s) 1. This case shows typical clinical presentation, morphology and immunophenotype of classic Hodgkin lymphoma (CHL) except for the lack of CD30 expression. The absence of CD30 expression is unusual in CHL, having been reported in fewer than 5% of cases. CD30 negativity in a suspected case of CHL necessitates careful consideration of alternative diagnoses, including mediastinal grey zone lymphoma (MGZL) and the rare entity of PAX5-positive anaplastic large cell lymphoma (ALCL). MGZL is unlikely because of the lack of expression of most B-cell markers except PAX5, indicating loss of the B-cell programme in the large neoplastic cells. PAX5+ ALCL can be negative for ALK1 but they are usually positive for CD30 and express one or more T-cell markers 2. Loss of CD30 expression also raises important questions regarding technical versus true biological antigen loss, prompting further consideration of its biological significance and the potential implications for CD30-targeted therapies.

References:

1. O'Malley DP, et al. American Registry of Pathology Expert Opinions: Immunohistochemical evaluation of classic Hodgkin lymphoma. *Ann Diagn Pathol.* 2019 Apr;39:105-110. PMID: 30802809.
2. Gru AA, et al. Best Practices in CD30 Immunohistochemistry Testing, Interpretation, and Reporting: An Expert Panel Consensus. *Arch Pathol Lab Med.* 2023 Jan 1;147(1):79-86.

Panel Diagnosis: Classic Hodgkin lymphoma (EBV-negative) with unusual immunophenotype (CD30 negative)

EA4HP26-LYWS-111

PAX5-negativity in classic Hodgkin lymphoma - does it exist?

Prof. Falko Fend¹, Dr. Jan Bosch-Schips¹

¹ University Hospital Tuebingen, Pathology, Tuebingen, Germany; ² University Hospital Tuebingen, Pathology, Tuebingen, Germany

Case Description

This 62-year-old male developed right inguinal and iliacal lymphadenopathy in 10/2018. No B-symptoms, normal blood counts.

01/2019: excisional biopsy of 4.3 cm inguinal lymph node was performed (submitted specimen). Following diagnosis, the patient did not undergo treatment for lymphoma and remained in good health.

Two years later, re-biopsy was performed from same location due to progressive lymphadenopathy (multiple nodes up to 4.3 cm), with virtually identical findings. BM biopsy remained uninvolved. Imaging revealed stage IIA. The patient underwent 2 cycles of ABVD and involved field RT and went into complete remission.

Biopsy Fixation Details

4.3 cm inguinal lymph node, formalin fixation.

Frozen Tissue Available

no

Details of Microscopic Findings

Disrupted lymph node architecture with nodularity created by expanded follicles, sometimes with regressed germinal centers, others resembling progressively transformed germinal centers. Within and surrounding the nodules, there are variably abundant atypical large cells, mostly mononuclear, some multinucleated giant cells. Occasional clusters of atypical cells can be observed. The nuclei are round to oval, nucleoli are medium to large size, prominent eosinophilic, viral inclusion-like nucleoli are mostly absent. The cells show moderate eosinophilic cytoplasm.

Occasional mummified cells. the background is dominated by small lymphocytes, some histiocytes and only rare eosinophils, no necrosis.

Immunophenotype

Large cells positive for: CD30, CD15, MUM1, EMA, TIA1 (heterogeneous), PD-L1 (heterogeneous), rare cells positive for Granzyme B and Perforin.

Large cells negative for: PAX5, CD2, CD3, CD4, CD5, CD8, B-F1, TCRdelta, CD45, ALK, EBV LMP1, CD20, CD79a, GATA3, CD21, CD23, ICOS, PD1, BCL6.

Background dominated by B cells with regular phenotype (both in germinal centers and follicle mantles), Tumor cells within and surrounding follicular structures with expanded CD23+ FDC networks and rosetted by CD3+, PD1+/- cells, moderate amounts of cytotoxic T-cells.

Cytogenetics

n.d.

Molecular Studies

B- and T-cell clonality studies (bulk tissue) rendered polyclonal results. FISH for JAK2 and DUSP22 breaks negative. NGS studies will be performed.

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-rich, PAX5-negative, architecturally mimicking NLPHL/NLPBL
versus

ALK-negative anaplastic large cell lymphoma with CHL-like features

Interesting Feature(s)

This case exhibits several unusual features, which raise questions concerning the differential diagnosis between classic Hodgkin lymphoma and peripheral T-cell lymphoma, especially ALK-neg. anaplastic large cell lymphoma. Whereas tumor cell morphology and distribution, with mostly single cells in a lymphocyte-rich background, as well as the strong co-expression of CD30, CD15 and MUM1 and the lack of T-cell surface markers and CD45 are favoring CHL, the complete lack of PAX5, strong positivity for EMA, as well as variable expression of cytotoxic markers favor ALK- ALCL. Similar cases in the literature have variably been classified as PAX5-neg. CHL (Asano N et al, 2011), PTCL (Huettl KS et al, 2019) and ALCL with CHL-like features (Bosch-Schips J et al, 2022). Whether these cases correspond to the few cases showing clonal T-cell rearrangement by single cell analysis and disputedly designated CHL of T-cell type (Müschen M et al, 2000) remains to be resolved.

Two further unusual aspects of this case are the architectural and cellular background in part reminiscent of NLPHL/NLPBL and the fact that the patient remained well for two years after lymph node excision without further therapy, with only slow progression of the disease.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV negative) with unusual phenotype (PAX5 negative), lymphocyte rich background mimicking NLPHL/NLPBL

Hodgkin-Type Richter Transformation, an uncommon evolution of CLL/SLL - a short case series

Prof. Beena Kumar¹, Dr. Pranav Dorwal², Dr. Paul Yeh³, Dr. Ravikiran Vedururu⁴, Broden Krause⁵, Dr. Ian Simpson⁶

¹ Beena Kumar, Monash Health Pathology, Clayton, Australia; ² Pranav Dorwal, Monash Health Pathology, Clayton, Australia; ³ Paul Yeh, Monash Health Pathology, Clayton, Australia; ⁴ Ravikiran Vedururu, Monash Health Pathology, Clayton, Australia; ⁵ Broden Krause, Monash Health Pathology, Clayton, Australia; ⁶ Ian Simpson, Monash Health Pathology, Clayton, Australia

Case Description

Two cases with almost similar history and pathological findings were presented to our hospital in 2025.

Case 1:

A 70-year-old female with widespread lymphadenopathy. No history of lymphoma.

PET Findings – Extensive metabolically active lymphadenopathy above and below diaphragm.

Case 2:

A 74-year-old male, a known case of CLL/SLL, not on treatment, presented with fevers and extensive lymphadenopathy.

PET Findings - Metabolically active lymphadenopathy most active in right inguinal and common iliac region.

Biopsy Fixation Details

The specimen was fixed in 10% formalin for 14 hours prior to processing.

Frozen Tissue Available

NA

Details of Microscopic Findings

Case 1:

The biopsy shows effaced nodal architecture. Population of relatively small lymphoid cells, with scattered large mononuclear cells. A few binucleated and mummified forms are also seen.

The large cells are positive for CD30 (Golgi pattern), CD15, PAX5 (dim) and OCT2, while being negative for CD3, CD20 and BOB1. A few of these are positive for EBV ISH.

The background lymphoid cells show CD5 and BCL2 positive B cells, while being negative for CD10, CD23 and SOX11.

Case 2:

The biopsy shows effaced lymphoid architecture. Mixed population of atypical lymphoid cells along with polymorphic infiltrate comprising lymphocytes, histiocytes, eosinophils and plasma cells and large cells resembling Hodgkin cells. There are some binucleated cells and multinucleated cells present.

The large cells show strong staining with CD30 and MUM1, focal CD15 positivity, weak to moderate positivity with PAX5, patchy EBV ISH positivity and negative with CD45.

There is a background population of CD20 positive cells which also co-express CD5 and CD23.

Immunophenotype

Case 1:

A monoclonal population of B-cells: CD19(+), CD5(+), CD10(-), CD20(+), CD22 dim(+), CD23(-), CD38(-), CD200(+), FMC7(+) and kappa light chain expression, consistent with a CD5(+) B-cell lymphoma.

Case 2: A monoclonal population of B-cells: CD19(+), CD5(+), CD10(-), CD20dim(+), CD22(+), CD23(+), CD38dim(+), CD200(+), FMC7(-) and lambda light chain expression, consistent with a B-cell lymphoma.

Cytogenetics

Normal cytogenetics

Molecular Studies

Pan Haematology Comprehensive Genomic Profiling Assay (Pan Haem 187 gene Panel)

Case 1 : pathogenic *TP53* variant is consistent with RT.

Case 2 : multiple somatic variants identified in *NF1*. Although somatic *NF1* variants are rarely observed in lymphoma, as a tumour suppressor gene, it is recurrently mutated in other solid malignancies.

Molecular features of cases show variants in tumour suppressor genes highlighting the heterogenous molecular profile that may occur in Hodgkin variant of RT.

Proposed Diagnosis

Case 1:

Classic Hodgkin lymphoma type Richter's transformation (CHL-RT).

Case 2:

Classic Hodgkin lymphoma type Richter's transformation (CHL-RT).

Interesting Feature(s)

Hodgkin lymphoma (HL) represents a rare (<1%) but recognized form of RT.

Recurrent molecular findings in RT include somatic aberrations in genes such as *TP53*, *NOTCH1* and *MYC*.

In Case 1, the detection of a pathogenic *TP53* variant is consistent with RT.

In Case 2, there were multiple somatic variants identified in *NF1*. Although somatic *NF1* variants are rarely observed in lymphoma, as a tumour suppressor gene, it is recurrently mutated in other solid malignancies.

In summary, the molecular features of our 2 cases show variants in tumour suppressor genes and highlight the heterogenous molecular profile that may occur in Hodgkin variant of RT.

Panel Diagnosis: Hodgkin variant of Richter transformation

EA4HP26-LYWS-120

Nodular sclerosis classic Hodgkin lymphoma with cytotoxic phenotype

Dr. Mikk Abram

North Estonia Medical Centre, Pathology Department, Tallinn, Estonia

Case Description

The patient is a 33-year-old female who presented with fatigue, pruritus, a skin rash on the legs, joint stiffness, night sweats, and inguinal lymphadenopathy of 6 months' duration. Computed tomography revealed lymphadenopathy in the cervical, paraaortic, iliac, and inguinal regions. A supraclavicular lymph node was excised and submitted for hematopathologic examination.

Biopsy Fixation Details

The lymph node was received fresh. After sectioning, one tissue fragment was submitted for flow cytometry and one fragment was frozen. The remaining tissue was fixed in formalin for histologic evaluation.

Frozen Tissue Available

Yes.

Details of Microscopic Findings

The lymph node demonstrated sclerosis with nodular architecture. The nodules were composed of lymphocytes, reactive follicles, histiocytes, eosinophils, neutrophils, and scattered large atypical cells, which were present singly and in clusters. These atypical cells showed one or multiple pleomorphic vesicular nuclei with prominent nucleoli, consistent with Hodgkin/Reed–Sternberg cells.

Immunophenotype

Immunohistochemistry: CD30+, CD15+, MUM1+, EMA+, CD4+, TIA1+, Perforin+, BOB1+/- (weak, partial), CD45-, OCT2-, BSAP/PAX5-, CD20-, CD79a-, CD3-, EBV/LMP1-, ALK-, CD2-, CD5-, CD8-, Granzyme B-, EBER-CISH-.

Flow cytometry: Negative for non-Hodgkin lymphoma (markers analyzed: CD45, CD19, CD20, κ, λ, CD3, CD4, CD8).

Cytogenetics

Not performed.

Molecular Studies

PCR-based clonality analysis (IdentiClone™) for clonal rearrangements of the IGH, IGK, IGL, TCRG, and TCRD loci was negative. Analysis of the TCRB locus was unsuccessful. Testing was performed on unfixed frozen tissue.

Proposed Diagnosis

Nodular sclerosis classic Hodgkin lymphoma with cytotoxic phenotype.

Interesting Feature(s)

The absence of BSAP/PAX5 expression and the expression of cytotoxic markers, EMA, and CD4 raise the differential diagnosis of peripheral T-cell lymphoma, particularly anaplastic large cell lymphoma. However, features supporting a diagnosis of classic Hodgkin lymphoma include BOB1 and CD15 expression, the absence of a sinusoidal growth pattern, and the lack of detectable clonal T-cell receptor rearrangements.

Panel Diagnosis: Nodular sclerosis Classic Hodgkin lymphoma with cytotoxic phenotype (due to absent B-cell clonality detection); NGS pending as features suggestive of ALK-negative anaplastic large cell lymphoma

EA4HP26-LYWS-124

Classic Hodgkin Lymphoma masked by non-necrotizing granulomatous inflammation with multinucleated giant cells

Dr. Anna Shestakova¹, PhD/MD student Nicolas Ulrich², Dr. Kate Parkinson¹, Dr. Anton Rets¹

¹ University of Utah and ARUP, Pathology, Salt Lake City, USA; ² University of Utah, School of Medicine, Salt Lake City, USA

Case Description

The patient is a 69-year-old woman with a 5-year history of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with mutated IGHV and del(13q), initially treated with bendamustine, rituximab, and ibrutinib. The patient developed disease progression, with PET/CT demonstrating diffuse lymphadenopathy concerning for Richter transformation. Initial axillary and iliac lymph node biopsies showed necrotizing granulomatous inflammation, prompting an additional biopsy. The subsequent inguinal lymph node biopsy revealed coalescing non-necrotizing granulomata with multinucleated giant cells containing polarizable material, rare eosinophils, and scattered atypical large cells positive for CD30, variable PAX5, and MUM1. Concurrent bone marrow biopsy demonstrated atypical CD30-positive cells within lymphohistiocytic aggregates, consistent with Classic Hodgkin lymphoma. Patient was treated with AAVD per the ECHELON-1 protocol and is currently in remission.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

no

Details of Microscopic Findings

Histologic sections demonstrate effaced lymph node architecture with numerous histiocytes coalescing into poorly formed granulomata, multinucleated giant cells containing polarizable material, along with scattered small, mature-appearing lymphocytes, rare eosinophils, and very rare admixed atypical large cells.

Immunophenotype

Flow cytometry: lambda-restricted CD5+ B cell population with phenotypic features most consistent with CLL/SLL.

Immunohistochemistry: Atypical cells positive for CD30, PAX5 (strong to dim), MUM1; negative for **CD3**, **CD20**, CD15, ALK1, and Epstein-Barr virus RNAs (EBER) by in situ hybridization.

Cytogenetics

Lymph node: not performed

Involved bone marrow: normal karyotype 46,XX

Molecular Studies

Lymph node: not performed

Involved bone marrow: NGS sequencing demonstrated pathogenic DNMT3A c.2339T>C, p.Ile780Thr VAF 4.5%

Proposed Diagnosis

Classic Hodgkin Lymphoma

Interesting Feature(s)

Classic Hodgkin lymphoma in the setting of CLL/SLL obscured by extensive non-necrotizing granulomatous inflammation, prominent multinucleated foreign-body-type giant cells, admixed with rare atypical large cells (Reed/Sternberg variants).

Panel Diagnosis: Hodgkin variant of Richter transformation

EA4HP26-LYWS-128

Classical Hodgkin Lymphoma, Nodular Sclerosis Type (rare CD30-negative variant)

Prof. Ingrid Simonitsch-Klupp¹, Prof. Ilse Oschlies², Dr. Christoph Semmelweis³, Prof. Wolfram Klapper²

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Case Description

Medical history:

61 year old male patient with inguinal lymphadenopathy,

Lymph node extirpation inguinal

- No additional lymphoma manifestations on CT (thorax and abdomen)
- Clinical stage I
- bone marrow biopsy negative
- Initiation of ABVD chemotherapy
- PET-CT restaging after completion of cycle 2: no residual lymphoma
- Involved-field radiotherapy administered with a total dose of 20 Gy
- Follow up: Ongoing complete remission (+6 years)

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

-

Details of Microscopic Findings

- Lymph node architecture completely effaced; nodular pattern with broadsclerotic bands
- Atypical mononuclear cells with vesicular nuclei, prominent nucleoli, and often pale, retracted cytoplasm (lacunar-

type cells, frequent typical Hodgkin-cells)

- Occasional multinucleated forms present (Reed-Sternberg cells)
- Background: predominantly small lymphocytes and numerous histiocytes; few eosinophils

Immunophenotype

Immunophenotype of H- and RS- cells:

Weak PAX5 expression; partial weak CD79a positivity

MUM1 positive; CD15 focally positive, PD-L1 positive

EMA patchy positivity

PRAME positive, CT45/Ki-A10 positive

Negative for CD30, CD20, CD19, CD3, CD2, CD23, BOB1, LMP1, OCT-2, CD45; EBER ISH negative, Kappa and Lambda ISH negative (RNAscope)

(CD30 performed on all blocks, stainings performed in both Pathology departments Vienna and Kiel independently)

Ki-67 ~60% in lesional cells

Cytogenetics

-

Molecular Studies

FISH with probes against:

CD274 (PDL1)/PDCD1LG2 (PDL2): 2-4 signals (2-4 signals also found with centromere probe

9; hence no amplification, rather polysomy)

IGH: (5'IGH, 3'IGH) 2-5 signals, no break

IGκ : (5'IG κ, 3'IG κ) 2-5 signals, no break

IGλ : (5'IG λ, 3'IG λ) 2-5 signals, no break

Clonality analysis (using Biomed 2 primers after microdissection of blast-cell rich areas):

no clonal IgH- and Ig κ gene rearrangements

Further analyses under progress (CD30 RNA-ISH expression analysis planned)

Proposed Diagnosis

Classical Hodgkin Lymphoma, Nodular Sclerosis Type (rare CD30-negative variant)

Interesting Feature(s)

- CD30 is a hallmark marker of cHL, but only very rare cases with absent or very low expression have been documented (PMID 9327746, PMID 9777980, PMID 40907344, PMID 27020217)
- Diagnoses in these instances depend heavily on morphology and other markers such as CD15, PAX5, EBV status, and broader immunoprofiles
- Technical factors (antigen retrieval, antibody clone) can influence detection and may underlie some CD30-negative results (PMID: 37377225)
- Decreased CD30 expression may also be observed after certain therapies (e.g., anti-CD30 antibody therapy, CAR-T-cell therapy), further complicating interpretation
- Besides CD30-negativity, unusual EMA-expression was also noted in this case

Panel Diagnosis: classic Hodgkin lymphoma (EBV-negative) with unusual phenotype (CD30 negative), nodular sclerosis

EBV+ DLBCL versus Hodgkin's lymphoma

Dr. Maja Nilsson Fors

University hospital of Umeå, Hematopathology department, Umeå, Sweden

Case Description

- 52-years old male with ankylosing spondylitis treated with Remicade(TNF-alfa blockade).
- The treatment was paused in May because of B-symptoms.
- PET-scan showed generalized lymphadenopathy and increased uptake in the bone marrow.
- Biopsy from abdominal lymph node and bone marrow biopsy was taken in September 2025.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No frozen tissue available.

Details of Microscopic Findings

Scattered HRS-like cells with enlarged nuclei with prominent nucleoli including cells with multiple nuclei and bilobed Reed-Sternberg like cells.

Background of small lymphoid cells and aggregates of histiocytic cells.

Immunophenotype

Positive expression: CD30/CD15/PAX-5/CD20/CD79a/MUM-1/OCT-2/EBER

Negative expression: CD45/ALK-1/CD10/BCL2/BCL6/CYCLIND1/CD10/BOB-1

Cytogenetics

No rearrangement of MYC, BCL6 or BCL2.

Molecular Studies

No molecular studies were performed.

Proposed Diagnosis

The atypical immunophenotype made the lymphoma hard to subclassify. The case was signed out as an EBV+ Diffuse Large B-cell lymphoma with a note that Classic Hodgkin's lymphoma could not be ruled out.

Interesting Feature(s)

The expression of CD20/CD79a/OCT-2 ought to be rare in Classic Hodgkin's lymphoma. CD20 can be expressed in 30-40% of cases but usually only on a minority of the neoplastic cells. CD79a expression is rare. OCT-2 and BOB-1 are usually not expressed but can more often be expressed in the lymphocyte rich subtype. CD15 can be expressed in 25% of cases of EBV+ DLBCL.

Panel Diagnosis: Classic Hodgkin lymphoma (EBV positive) with unusual phenotype

Classic Hodgkin lymphoma, lymphocyte-rich variant with TFH cell enriched background

Dr. Dominik Nann, Dr. Antonio Vogelsberg, Prof. Falko Fend

University Hospital Tuebingen, Institute of Pathology, Tübingen, Germany

Case Description

A 33-year-old man suffered from night sweat and weight loss, and showed a cervical lymphadenopathy. The MRI analysis detected an enlarged lymph node of 2.8 cm. A core needle biopsy was without a conclusive diagnosis and an excision of the whole lymph node was performed.

Biopsy Fixation Details

4% buffered formalin, paraffin embedding

Frozen Tissue Available

-

Details of Microscopic Findings

There is an enlarged lymph node with abundant follicular structures, but also with an increased interfollicular zone with brighter areas. Some follicles showed well formed germinal centres, and some exhibit irregularly expanded mantle zones. In the interfollicular areas there are zones with histiocytic proliferations and eosinophilic granulocytes. Many Hodgkin cells are interspersed within the interfollicular areas as well as within the mantle zones. The cells are large with abundant cytoplasm, enlarged nuclei and prominent nucleoli.

Immunophenotype

The Hodgkin cells are: CD30 +, CD15 +, CD20 -, PAX5 weakly +, MUM1+, LMP1 -, MEF2B -, OCT2 -, BOB1 -, CD79A -, Kappa/lambda-ISH -. CD30 shows quite a lot of positive cells, including also smaller cells with a weak positivity. CD20 shows many B cells within the follicles and CD3 abundant T cells, especially in the interfollicular areas. There is also an increase of TFH cells with PD1, ICOS, and CXCL13 positivity, but without a clear positivity for BCL6 and CD10. CD10 only shows single positive cells outside of the positive germinal centre cells.

Cytogenetics

-

Molecular Studies

Clonality analysis:

IdentiClone® T Cell Receptor Gamma Gene Rearrangement Assay 2.0 (Invivoscribe), and IdentiClone® TCRB Gene Clonality Assay (Invivoscribe): no T cell clone

There is also no evidence for a B cell clone in the IG analysis (Biomed-2, FR1, FR2, FR3 and IGK primer set).

NGS analysis:

no mutation in *RHOA*, *IDH2*, *TET2*, *DNMT3A* (custom panel, Ion GeneStudio S5 Prime System, Thermo Fisher Scientific).

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-rich variant, EBV negative with enriched in TFH cells, but without any evidence for T-cell clonality or TFH lymphoma type mutations

Interesting Feature(s)

This is a typical case of a classic Hodgkin lymphoma, lymphocyte-rich variant. Additionally, this case shows many cells in the background with a TFH phenotype (PD1, ICOS, CXCL13), which is well described in B cell lymphomas including classic Hodgkin lymphoma, especially in lymphocyte-rich variant. This feature raises the differential diagnosis of a TFH lymphoma (especially TFH-lymphoma, follicular type), which can also harbour cells with Hodgkin/Reed-Sternberg-like morphology and immunophenotype. However, clonality and NGS analysis reveal no evidence of a T-cell lymphoma in the submitted case. The literature describes CD10 as a useful TFH marker in the differential diagnosis between TFH lymphoma and TFH cell rich background in other lymphomas, consistent with this, CD10 is also negative in our case. After ABVD therapy, the patient achieved complete remission.

Panel Diagnosis: Classic Hodgkin Lymphoma with TFH cell enriched background (subtype?)

Classic Hodgkin lymphoma with a predominantly germinotropic pattern

Dr. Luke Bushrow, Dr. Arwa Shana'ah, PhD/MD Yulan Jin

Ohio State Univeristy, Pathology, Columbus, Germany

Case Description

A 43-year-old female with no significant medical history presented with 6-month history of dyspnea, night sweats, and unintentional weight loss. CT imaging identified a 13 cm left upper lobe lung mass with extension into the anterior mediastinum and encompassing multiple large caliber arteries. PET imaging showed intense FDG avidity of the mass (18.7 SUV) and bilateral supraclavicular hypermetabolic lymphadenopathy (10.3 SUV). An initial left supraclavicular lymph node core needle biopsy was inconclusive. Subsequent excision was consistent with classic Hodgkin lymphoma.

The patient was started on nivolumab, doxorubicin, vinblastine, and dacarbazine (Nivo-AVD) regiment with resolution of type B symptoms. Interval PET imaging revealed a marked radiographic and metabolic response.

Biopsy Fixation Details

Lymph node tissue was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections show partially preserved lymph node architecture with numerous lymphoid follicles and attenuated sinuses. A majority of the lymphoid follicles display germinal centers overtaken by nodules of large cells with abundant cytoplasm, round to curved nuclei, vesicular chromatin, and prominent nucleoli. These nodules are cuffed by small lymphocytes with very rare eosinophils seen. Aggregates of plasma cells are noted in the interfollicular region.

Immunophenotype

By immunohistochemistry / in-situ hybridization:

- Positive: CD30 (strong), CD15 (subset, weak), PAX5 (dim), MUM1, CD4 (dim)
- Negative: ALK1, CD2, CD3, CD4, CD5, CD7, CD8, EMA, Granzyme B, HHV8, CD138, CD19, CD20, CD79a, CD43, CD45, EBER ISH, kappa/lambda light chain ISH, AE1/AE3, SOX10, S100, BCL6, CD21, CD23

Other IHC findings:

- CD21 highlights the follicular dendritic cell meshworks surrounding the nodules of lymphoma cells, consistent with a germinal center localization

Cytogenetics

46,XX[cp26]

Molecular Studies

Next generation sequencing panel detected no pathogenic somatic variants.

Polymerase chain reaction (PCR) analysis demonstrated polytypic patterns of T-cell receptor gamma (TCRG), T-cell receptor beta (TCRB), and immunoglobulin heavy chain (IgH).

Proposed Diagnosis

Classic Hodgkin lymphoma

Interesting Feature(s)

Although the immunophenotype and presentation are consistent with classic Hodgkin lymphoma (CHL), the distribution of the lymphoma cells and the lack of associated inflammatory milieu is unusual.

CD21 IHC demonstrates preferential localization of lymphoma cells within the germinal centers, suggesting possible tropism for the germinal center microenvironment [germinotropism]. The significance of this is unknown, but it may provide insight into the mechanism by which CHL cells spread.

The abnormally high density of Hodgkin/Reed-Sternberg cells arranged in micronodules without the typical inflammatory background is also unusual for CHL, except in the syncytial variant. This morphologic pattern may be encountered in other entities including anaplastic large cell lymphoma, KSHV/HHV8+ germinotropic lymphoproliferative disorder, microlymphomas in the setting of KSHV/HHV8-associated multicentric Castleman disease, and metastatic tumors. Accordingly, extensive immunophenotypic studies are required to establish the diagnosis.

Panel Diagnosis: classic Hodgkin lymphoma with predominant germinotropic pattern

EA4HP26-LYWS-152

Classic Hodgkin Lymphoma in a background of follicular helper T cells.

Dr. Sahil Chaudhary¹, Dr. Jinbo Fan¹, **Dr. Ifeyinwa E. Obiorah**¹

¹ University of Virginia Health, Charlottesville, USA; ² University of Virginia Health, Charlottesville, USA

Case Description

The patient is a 74-year-old man who initially noted left groin swelling following a fall. Evaluation in the emergency department revealed left inguinal lymphadenopathy on cross-sectional imaging. A subsequent core needle biopsy demonstrated a lymphoproliferative disorder but was non-diagnostic. He was later evaluated by hematology/oncology, who recommended an excisional biopsy for definitive diagnosis. The patient denied weight loss, fevers, chills, chest pain, shortness of breath, nausea, vomiting, dysuria, abdominal pain, or chronic leg pain, and reported remaining physically active with daily gym exercise

Biopsy Fixation Details

The lymph node is fixed in formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the inguinal lymph node show nodal architectural effacement with prominent bands of dissecting fibrosis and mildly thickened capsule. There is a nodular proliferation of large atypical cells with abundant clear to amphophilic cytoplasm, irregular nuclei, vesicular chromatin and variably prominent nucleoli, morphologically resembling lacunar cells and classic Hodgkin/Reed-Sternberg morphology. The background shows inflammatory cells consisting of predominantly small lymphocytes, histiocytes, plasma cells and scattered eosinophils.

Immunophenotype

The large atypical cells are positive for PAX5 (dim), CD30, CD15 (weak and focal), MUM1 and negative for CD20, OCT2, BOB1 and ALK1. CD3 stain background T cells, some forming T cell rosettes. A subset of the T cells is positive for ICOS, BCL6, and CXCL13 with much fewer cells staining with PD1 and CD10. EBV RNA stain is negative.

Cytogenetics

FISH studies were negative for MYC, BCL2, BCL6 and DUSP22 gene rearrangements.

Molecular Studies

PCR studies detected no clonal T cell receptor or immunoglobulin heavy chain gene rearrangements.

Proposed Diagnosis

Classic Hodgkin lymphoma, nodular sclerosis subtype with background follicular helper T cells.

Interesting Feature(s)

The patient presented with isolated inguinal lymphadenopathy discovered after a fall and lacked B symptoms or functional decline, highlighting an indolent and incidental presentation of classic Hodgkin lymphoma in an older, physically active individual.

The large atypical cells demonstrated a classic cHL immunoprofile (CD30+, weak/focal CD15+, dim PAX5+, EBV-

negative) with loss of B-cell transcription factors, reinforcing the diagnosis despite prior non-diagnostic core biopsy. The presence of ICOS-, BCL6-, and CXCL13-positive background T cells raises diagnostic complexity and highlights the role of the tumor microenvironment in cHL, particularly in cases that may mimic TFH-associated lymphomas.

Panel Diagnosis: classic Hodgkin lymphoma NS EBV-

EA4HP26-LYWS-167

Relapsed Classical Hodgkin Lymphoma With Aberrant Cytotoxic Marker Expression

Dr. Marie Donzel^{1,2}, Dr. Juliette Fontaine¹, Dr. Gabriel Anthérieu³, Prof. Alexandra Traverse-Glehen^{1,2}

¹ Hospices Civils de Lyon, Pathology, Lyon, France; ² Université Claude Bernard Lyon 1, Lyon, France; ³ Hospices Civils de Lyon, Hematology, Lyon, France

Case Description

An 80-year-old patient presented with deterioration of general condition, fever, and diarrhea. PET-CT showed bilateral cervical hypermetabolic lymphadenopathy (SUVmax 19.5), and a cervical lymph node biopsy established classical Hodgkin lymphoma, EBV-negative and without cytotoxic marker expression. The patient received five cycles of PVAB, achieving a complete metabolic response.

One year later, experienced a relapse with similar systemic symptoms and erythematous eruption. PET-CT suggested multisystem relapse involving nodes, lung, liver, and bone (maximum SUV 18.8). A left cervical biopsy was performed.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

Histological examination showed effacement of the lymph node architecture by a polymorphous inflammatory infiltrate within a scleronodular framework rich in eosinophils. Numerous large atypical cells with abundant eosinophilic cytoplasm and ovoid or bilobed nuclei containing prominent nucleoli were identified, consistent with Hodgkin cells.

Immunophenotype

The large cells expressed CD30, MUM1 and CD15. They lacked expression of B-cell markers (PAX5, CD20, CD79a, CD19, OCT2, BOB1, PU1) and ALK1. The background consisted of T lymphocytes (70% CD4 and 30% CD8), without loss of pan-T-cell markers. The large cells expressed EMA and GATA3 and showed strong and diffuse expression of perforin with partial expression of granzyme B. TIA1 was negative. EBER was negative.

Cytogenetics

N/A

Molecular Studies

Clonality analysis (BIOMED-2) demonstrated a clonal rearrangement on a background of irregular polyclonality, suggesting the presence of a monoclonal T-cell population, associated with a minor monoclonal B-cell population. NGS highlighted an isolated variant of *BTK*.

RNA sequencing is ongoing to assess for a potential *JAK2* rearrangement.

Proposed Diagnosis

Relapsed classical Hodgkin lymphoma with aberrant cytotoxic expression.

The patient is currently in complete remission following immunotherapy with anti-PD1 (pembrolizumab) combined with Ruxolitinib.

Notably, given a concurrent cutaneous eruption, a skin biopsy was performed, showing loss of the granular layer with compact parakeratosis and no suspicious lymphocytic infiltrate, raising the possibility of an ichthyosiform syndrome.

Interesting Feature(s)

This case illustrates a relapsed classical Hodgkin lymphoma (cHL) with aberrant expression of cytotoxic markers. Expression of cytotoxic molecules has been previously reported in cHL, typically in cases lacking PAX5 and CD20 expression and without T-cell receptor (TCR) rearrangements. However, cases with documented TCR rearrangements are rare, and most have been interpreted as T-cell lymphomas with Hodgkin-like features. In our case, a clonal TCR gamma rearrangement was identified on a background of irregular polyclonality, suggesting the presence of a monoclonal T-cell population ; but interpretation of such population is challenging in an 80-year-old patient due to potential age-related restriction of the immune repertoire. In addition, a minor monoclonal B-cell population was detected, supporting the diagnosis of cHL.

The presence of an ichthyosiform syndrome, previously reported in association with Hodgkin lymphoma, provided an additional supportive argument for the diagnosis of Hodgkin lymphoma.

These features emphasized the importance of integrating clinical, histological and molecular data in the assessment of atypical presentations of cHL.

Panel Diagnosis: Relapsed classic Hodgkin Lymphoma with unusual phenotype (cytotoxic markers) and T cell clone

EA4HP26-LYWS-172

Classic Hodgkin lymphoma with interfollicular pattern and Castleman-like features

Dr. Miekian Stonhill, Dr. Phillip Michaels

Mass General Brigham, Pathology, Boston, USA

Case Description

A previously healthy 23-year-old woman presented to primary care clinic with fatigue, weight loss, and fevers. Laboratory testing showed markedly elevated ESR (110 mm/h) and CRP (118 mg/L), and imaging showed supradiaphragmatic lymphadenopathy. A core biopsy of an axillary lymph node was obtained and was nondiagnostic. Subsequently, an excisional biopsy of an axillary node was performed, and yielded a diagnosis of classic Hodgkin lymphoma with unusual interfollicular architecture. The patient began treatment with nivolumab, doxorubicin, vinblastine, and dacarbazine (nivo-AVD), with interim PET scan showing complete response.

Biopsy Fixation Details

Formalin and B-plus

Frozen Tissue Available

No

Details of Microscopic Findings

Sections showed overall preserved lymph node architecture with reactive follicles as well as atretic follicles with perforating vessels. Twinning of germinal centers and focal concentric arrangements of mantle zone lymphocytes were noted. The interfollicular areas showed vascular hyperplasia and contained sheets of plasma cells, a mixed population of small lymphocytes with rare histiocytes and eosinophils, and singly scattered large lymphoid cells. The large cells exhibited abundant pale cytoplasm and irregular nuclei with vesicular cytoplasm and prominent eosinophilic nucleoli. Some large cells showed multinucleation or hyperchromasia ("mummified" appearance).

Immunophenotype

Large cells were positive for CD30, PAX5 (weak), CD15, and MUM1, and negative for CD20, OCT2, BOB1, EBER, and HHV8. Non-neoplastic follicles showed a normal immunophenotype and were associated with follicular dendritic cells. Interfollicular T cells showed preserved expression of pan-T-cell antigens and a normal CD4:CD8 ratio, and plasma cells were polytypic. No abnormal B or T-cell population was detected by flow cytometry.

Cytogenetics

No metaphases obtained

Molecular Studies

None

Proposed Diagnosis

Classic Hodgkin lymphoma, interfollicular pattern

Interesting Feature(s)

In this case, the lymph node appeared overall architecturally normal with Hodgkin/Reed-Sternberg (HRS) cells present in interfollicular areas; this pattern of growth has been described in a small subset of cases, mostly mixed cellularity cHL (PMID: 29566944). In this case, a core biopsy was nondiagnostic due to the relative rarity of HRS cells and the overall architectural preservation; cases of cHL with this architecture may pose a diagnostic challenge. Interfollicular areas also showed marked plasmacytosis and hypervascularity. Follicles showed a variety of morphologies including atretic follicles with multiple small germinal centers ("twinning"), perforating vessels, and expanded mantle zones, as well as irregularly enlarged follicles with hyperplastic germinal centers.

Similar morphology has previously been reported in small case series, often in association with HHV8-negative plasma cell or mixed Castleman disease (PMID: 32152665). This pattern has been associated with IL-6 dysregulation, and in some cases, was associated with elevated serum IL-6 and positive IL-6 expression by immunohistochemistry on Reed-Sternberg cells. While IL-6 levels were never directly tested in this case, inflammatory markers (ESR, CRP, haptoglobin, serum immunoglobulins) were elevated, suggesting a systemic inflammatory state in the absence of clear autoimmune or infectious disease. While outcome data on similar cases is limited, the potential association with IL-6 signaling raises the possibility of anti-IL-6 agents such as tocilizumab as targeted therapies for these cases.

Panel Diagnosis: Classic Hodgkin Lymphoma with Castleman like features asking for a Castleman disease association

EA4HP26-LYWS-182

A case of MAL1+ Diffuse Large B-Cell Lymphoma arising in an eosinophil, T-cell and histiocyte rich background

Dr. Dexter Kirk, Dr. Sarah DePew

University of Tennessee Health Science Center College of Medicine, Pathology, Knoxville, USA

Case Description

A 42-year-old man recently refugee from South America with intermittent fevers and fatigue presents with a one-year history of swelling in the neck. Notable laboratory values at presentation to our institution included leukocytosis (WBC 18.8 k/ μ L) secondary to neutrophilia, lymphocytosis and eosinophilia. Extensive infectious workup did not uncover evidence of parasitic or fungal infection. CT scans showed bulky lymphadenopathy throughout the neck, upper mediastinum, and mesentery as well as splenomegaly. Excisional biopsy was performed which showed CD20-positive large B-cells in a background of predominantly eosinophils, T-cells, and histiocytes. Final integrated diagnosis after additional studies was diffuse large B-cell lymphoma, NOS. Subsequent bone marrow biopsy demonstrated involvement (~20%). The patient was treated with chemotherapy and had clinical course complicated

by sepsis, hypotension requiring vasopressors and ultimately disease progression. Nearly six months after diagnosis, the patient pursued hospice care.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

Cervical lymph nodes excisional biopsy demonstrates architecture completely effaced by large, immunoblastic-like lymphocytes with prominent nucleoli and a scant-to-moderate amount of eosinophilic cytoplasm. Large neoplastic B-cells form two distinct patterns: 1) Clustered and forming discrete large nodules and 2) scattered singly throughout a dense inflammatory background consisting predominantly of eosinophils, small T-cells and histiocytes with rare giant cells seen. Occasional Hodgkin/Reed-Sternberg-like cells are identified.

Immunophenotype

By immunohistochemical stains, the large atypical cells are positive for CD20 (strong), PAX5 (weak), CD30 (weak), CD45, CD23 (subset), CD79a, BCL2, CD43, MUM1, and MAL1. There is scattered staining of c-MYC and CD5. The atypical cells are negative for CD3, CD4, CD7, CD8, BCL6, CD10, CD15, Cyclin D1 and EBER in-situ hybridization study. CD21 shows disrupted/absent follicular dendritic cell meshworks. By flow cytometric analysis, a population of abnormal B-cells is detected (8.5%) which is positive for CD20, CD19, CD43, CD23, and CD38 and negative for CD5, CD10 and surface light chain expression. Background T-cells showed no aberrancy by immunohistochemical stains or flow cytometric analysis.

Cytogenetics

FISH panel targeting alterations seen in aggressive B-cell lymphoma detected a BCL6 rearrangement in 35% of nuclei. This test was negative for rearrangements of BCL2, MYC, and for t(11;14) IGH::CCND1.

Molecular Studies

Not performed

Proposed Diagnosis

Although several different entities were considered including classic Hodgkin lymphoma, T-cell histiocyte rich large B-cell lymphoma (THRLBCL), primary mediastinal large B-cell lymphoma (PMBL) and gray zone lymphoma (GZL), taking all the clinical, immunophenotypic, and cytogenetic features of this tumor in mind, final proposed diagnosis was **diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)** with a non germinal-center/activated phenotype.

Interesting Feature(s)

- This case has an eosinophil, T-cell and histiocyte rich background. In particular, tissue eosinophilia is quite uncommon for large non-Hodgkin B-cell lymphoma and more commonly seen in entities such as classic Hodgkin lymphoma and T-cell lymphomas.
- B-cells in this case have a phenotype (CD23+, weak CD30+, MAL1+, slg-) which is commonly associated with primary mediastinal large B-cell lymphoma (PMBL-like), but presented with radiologic concern for extrathoracic disease, splenomegaly and a BCL6 rearrangement more consistent with DLBCL.

Panel Diagnosis: no classified no pictures

38-year-old HIV patient with classic Hodgkin lymphoma (cHL) associated with fulminant hemophagocytic lymphohistiocytosis (HLH)

Dr. Ling Zhang, Dr. Mohammad Hussaini

Moffitt Cancer Center, Hematopathology, Tampa, USA

Case Description

A 38-year-old white male was diagnosed with HIV in 2012 and has been treated with Biktarvy since 2021 with good control. In December 2025 he collapsed and presented with 40-pound weight loss, progressive fatigue, and fevers to 102° F. Epstein-Barr virus (EBV) viremia was noted (plasma EBV by Quantitative NAAT of 7000 IU/ml). Outside CT scan showed lymphadenopathy and hepatosplenomegaly. He was transferred to us for diagnosis. In-house laboratory data showed Hgb of 6.9 g/dl, platelets of 38K/uL, normal WBCs, elevated ferritin (12294 ng/mL), LDH (238 U/L), ALK 707 U/L, IgE (8537 kU/mL), and elongated PT (30.2 sec) and aPTT (39.5 sec). HIV and CMV were not detected. Biopsies of a right neck lymph node (LN) and bone marrow (BM) were performed.

Biopsy Fixation Details

LN: 10% formalin

BM: B plus Fix (BBC) fixative

Frozen Tissue Available

NA

Details of Microscopic Findings

LN: H&E slides showed an atypical infiltrate with inflammatory cells as well as numerous large, atypical lymphoid cells with enlarged nuclei, prominent nucleoli, and abundant amphophilic cytoplasm, consistent with Reed-Sternberg (RS) cells and variants.

BM (at diagnosis): aspirates included a mixture of hematopoietic precursors. Occasional histiocytes engulfing hematopoietic elements are identified. BM core biopsy was largely replaced by Hodgkin cells surrounded by epithelioid histiocytes, fibrosis, and inflammatory cells. Residual trilineage hematopoiesis was noted and focally, histiocytes with hemophagocytosis were observed.

BM (post-therapy): The aspirate and core biopsy revealed sheets of atypical, enlarged histiocytes, with prominent hemophagocytosis. Small foci of residual Hodgkin cells were present.

Immunophenotype

LN: The Hodgkin cells were positive for CD30, CD15, PAX-5, MUM1, BCL-6 and EBER and negative for CD45, CD20 and ALK1. Background CD3/CD5 positive T-cells and scattered PD1 positive cells were present.

BM (at diagnosis and post-therapy): The Hodgkin cells showed identical IHC findings to lymph node. CD68 highlighted aggregated histiocytes, some displaying hemophagocytosis.

Cytogenetics

BM: 46,XY[20]

Molecular Studies

Bone marrow: PCR for B-cell gene rearrangement failed. MLAP (523-gene DNA/RNA NGS panel): negative.

Proposed Diagnosis

Classic Hodgkin lymphoma (cHL) with HLH (Hemophagocytic Lymphohistiocytosis)

Interesting Feature(s)

Composite cHL and HLH involving LN and BM in a patient with history of HIV and recent EBV reactivation is rare. CD15 positivity and absent CD20 and CD45 expression argue against EBV+ DLBCL. HLH is rare, hyperinflammatory syndrome leading to cytokine storm, organ damage, and multi-organ failure that could be potentially fatal. It is commonly triggered by infection, autoimmune, or malignancy and often accompanied by positive EBV status. Of malignancy-triggered HLH 6% occur in cHL (PMID: 26314082). Our patient's clinical picture is more representative of severe form of HLH manifested with pancytopenia, coagulopathy, hepatopathy, hemophagocytosis, and neurologic

dysfunction (PMID: 34605776, 38066877). Cytokines, chemokines, and growth factors (e.g., IL6, CCL5, CCL17, and TGF- β) from cHL created a positive inflammatory loop and resulted in uncontrolled macrophage activities in our patient (PMID: 38092473). Concurrent elevated EBV viremia and elevated IgE levels indicate involvement of multiple complex immune pathways resulting in aggressive clinical behavior. Our patient passed away 21 days after initial diagnosis.

Panel Diagnosis: Classic Hodgkin lymphoma (EBV-positive) with fulminant HLH, immune deficiency/immune dysregulation-associated (HIV-infection)

EA4HP26-LYWS-194

Classic Hodgkin lymphoma with aberrant T-cell antigen expression

PhD/MD Sehbali Arslankoz¹, PhD/MD John R. Goodlad²

¹ Ankara Etlik City Hospital, Pathology, Ankara, Turkey; ² NHS Greater Glasgow and Clyde, Pathology, Glasgow, UK

Case Description

A 72-year-old male presented in September 2019 with persistent pyrexia, sterile blood cultures and cytopenia, in the context of a markedly elevated serum ferritin level (4598 ug/l), raising suspicion of haemophagocytic lymphohistiocytosis. As part of the diagnostic work-up, a bone marrow trephine biopsy was performed. PET-CT scan performed at the time revealed prominent PET avid nodes in the mediastinum and both supraclavicular regions. No lymph node biopsy was performed, but a diagnosis of classic Hodgkin lymphoma was made on the basis of the bone marrow appearances. The patient was treated with standard Hodgkin-type chemotherapy (six cycles of ABVD) with complete metabolic response. He remains in complete remission seven years after presentation.

Biopsy Fixation Details

The bone marrow trephine biopsy was fixed in 10% buffered formalin and decalcified using EDTA.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The bone marrow trephine showed hypercellular marrow (approximately 75%), with focal deposition of fine reticulin fibres in association with paratrabecular aggregates comprising a mixed inflammatory cell population, including small lymphocytes, histiocytes and granulocytes. There were also quite numerous, but individually scattered large cells with moderate amounts of cytoplasm, large vesicular nuclei and prominent eosinophilic nucleoli. Occasional cells with bilobed nuclei were identified although characteristic Reed-Sternberg cells were not seen. The background marrow showed trilineage haematopoiesis with prominent eosinophils, partially disrupted architecture and numerous histiocytes, several of which showed clear evidence of erythrophagocytosis, in keeping with the clinical suspicion of haemophagocytic activity.

Immunophenotype

The small lymphocytes were of T-lineage (CD3 positive). The large, atypical cells were positive for CD8, CD15, CD30, PAX5, and MUM1, and negative for CD3, CD4, CD20, CD79a, OCT2, BOB1, TIA1, granzyme B, ALK, CD33, CD34, CD42B, CD117, LMP1, and EBER.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

Classic Hodgkin lymphoma with aberrant expression of CD8, diagnosed on bone marrow biopsy.

Interesting Feature(s)

This case shows a bone marrow infiltrate with architectural and cytological features compatible with classic Hodgkin lymphoma, including a fibrotic background and a mixed inflammatory cell population containing scattered large, atypical cells. Despite the unusual immunophenotype with CD8 expression, a diagnosis of classic Hodgkin lymphoma was made since the neoplastic cells showed characteristic expression of CD15, CD30 and PAX5, and an absence of other B-cell and T-cell antigens, together with imaging studies confirming lymph node involvement.

Aberrant expression of T-cell antigens is a rare but well- documented occurrence in classic Hodgkin lymphoma. It is reported in approximately 5% of cases, most commonly CD4 and CD2, but also occasionally CD5 and/or CD8 [PMID: 16056244]. It represents a diagnostically challenging phenomenon, particularly with presentation in bone marrow, and has also been associated with inferior outcomes [PMID: 23305738].

Panel Diagnosis: classic Hodgkin lymphoma (EBV-negative) with aberrant T-cell-specific molecule expression- no subtyping as in bone marrow

EA4HP26-LYWS-196

CD30(+) Lymphoproliferative Neoplasm with T- and B-cell Antigen Expression

Dr. Tran Nguyen, **Dr. Elena M. Fenu**

Duke University Medical Center, Department of Pathology, Durham, USA

Case Description

An eight-year-old female presents with a one-month history of a tender left supraclavicular mass. The patient denies any other symptoms including fever, weight loss, or night sweats. Subsequent ultrasound and magnetic resonance imaging of the neck showed extensive left supraclavicular adenopathy with extension into the left axilla, with the largest lymph node up to 3.3 cm. An excisional biopsy of a left cervical lymph node was performed.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

The lymph node is enlarged, and normal architecture is effaced by bands of sclerosis and a mixed infiltrate of lymphocytes, histiocytes, and eosinophils. Occasional admixed atypical large cells are present, which show prominent nucleoli and rare bi- and multinucleation.

Immunophenotype

The large cells are positive for CD45(subset), PAX5(weak), CD79a(subset weak), CD30, CD15(subset weak), MUM1, and OCT2(subset weak); additionally, they show at least partial staining with CD3(subset), CD2, CD5, CD7(subset), and CD4. They are negative for ALK-1, CD8, BOB1, GATA-3, EMA, BCL6, and CD10. EBER CISH is negative. CD19 and CD20 demonstrate non-specific granular staining.

CD20 and other B-cell markers stain background small B-cells. CD3, CD2, CD5, and CD7 stain background small T-cells, which show a CD4:CD8 ratio of 5:1. CD21 shows focally disrupted follicular dendritic cell meshworks.

Cytogenetics

Not performed

Molecular Studies

A dominant monoclonal B-cell population is detected by next generation sequencing.

No monoclonal T-cell population detected by TCR beta chain or TCR gamma chain PCR.

Proposed Diagnosis

CD30-positive lymphoproliferative neoplasm, favor Classic Hodgkin lymphoma.

Interesting Feature(s)

The patient was treated with Hodgkin lymphoma-directed therapy. She received Nivolumab, Adriamycin, Vinblastine, and Dacarbazine (N-AVD) with interval resolution of her lymphadenopathy and no recurrence at 3- month follow-up. Neoplastic cells showed classic Hodgkin-like morphology with expression of multiple B- and T-cell markers, although many showed subset weak or granular/incomplete staining, making the diagnosis challenging. PAX5 expression has rarely been documented in anaplastic large cell lymphoma, however the presence of a detectable monoclonal B-cell population and the fact the patient responded to Hodgkin-directed therapy argue against a T-cell neoplasm. Expression of T-cell markers in Hodgkin lymphoma may be associated with worse prognosis.

Panel Diagnosis: Classic Hodkin Lymphoma (EBV-negative) nodular sclerosis with unusual phenotype

EA4HP26-LYWS-201

A different “gray zone”: a borderline case of lymphocyte-rich classic Hodgkin lymphoma versus nodular lymphocyte-predominant Hodgkin lymphoma

Dr. Miekan Stonhill, Dr. Sam Sadigh

MGB, Pathology, Boston, USA

Case Description

A 76-year-old man with past medical history of coronary artery disease, dermatomyositis, and Agent Orange exposure presented with a right parotid mass and palpable right cervical lymphadenopathy, present for several months and without associated systemic symptoms. Two FNA procedures were attempted, both demonstrating lymphocytes and felt to be most consistent with a reactive process. An excisional biopsy was then performed due to persistent adenopathy and was diagnostic of lymphoma. The patient was treated with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (BV-AVD), with end-of-treatment PET scan showing complete response.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

H&E sections showed an enlarged lymph node with complete architectural effacement by a nodular proliferation of predominantly small lymphocytes. There was no residual follicular architecture, and no germinal centers were seen. Scattered large, atypical lymphoid cells with abundant pale cytoplasm and irregular nuclei with vesicular chromatin and variably prominent nucleoli were present within nodules; a few forms were also noted in interfollicular areas. Most large cells were mononuclear, but a few binucleated forms consistent with Reed-Sternberg cells were seen. Eosinophils and histiocytes were not present in significant numbers, and there was no sclerosis or necrosis.

Immunophenotype

The large cells were positive for CD30, PAX5 (weak to moderate), MUM1, BCL6 (weak/subset), OCT2 (weak), and CD79a (variable) and were negative for CD15, CD19, CD20, BCL2, BOB1, CD45, and EBER. PD-1 and BCL6 showed T-cell rosette formation around large cells. The background lymphoid cells consisted of CD20+ B cells in nodules and CD3+ T cells predominantly between nodules. Nodules were associated with markedly expanded CD21+ follicular dendritic cell meshworks, which encompassed many of the large cells. Flow cytometry showed no clonal B-cell or unusual T-cell population.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-rich subtype (LR-CHL), nodular pattern

Interesting Feature(s)

This case showed features overlapping with those of nodular lymphocyte-predominant Hodgkin lymphoma/nodular lymphocyte-predominant B-cell lymphoma (NLPHL), creating diagnostic difficulty. Cases of this type have been described in the literature for decades, including cases of classic Hodgkin lymphoma with follicular or NLPHL-type architecture (PMID: 11789727); nodular pattern LR-CHL was previously termed “follicular Hodgkin lymphoma” and thought to represent an intermediate biologic entity between NLPHL and other CHL subtypes, or to represent an early stage of CHL (PMID: 19465900).

In this case, the overall architecture was more NLPHL-like; neoplastic cells were located within and between nodules of small B cells, which were associated with expanded follicular dendritic cell meshworks and did not contain residual germinal centers. The large cells included mostly mononuclear forms with few morphologically diagnostic Reed-Sternberg cells. They were strongly positive for CD30 and negative for CD45, but showed increased expression of B-cell markers compared to typical Hodgkin/Reed-Sternberg cells (moderate PAX5 expression; weak positive expression of CD79a, OCT2, and BCL6). The lymphocyte-rich subtype of classic Hodgkin lymphoma has been associated with higher expression of B-cell markers than other subtypes, and the overall immunophenotype in this case was considered to be most consistent with a diagnosis of CHL.

Panel Diagnosis: Classic Hodgkin Lymphoma Lymphocyte Rich with NLPHL pattern

EA4HP26-LYWS-204

TFH-rich classic Hodgkin lymphoma

Dr. Olga Kouroukli, Dr. Christos Masaoutis, PhD/MD Evdoxia Pouliou, M.Sc./M.A. Lamprini Vlachogianni, PhD/MD Elissavet Oikonomaki, Dr. Leonidas Marinos, Dr. Georgios Kanellis, Dr. Asimina Papanikolaou

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Case Description

We present the case of a 68-year old male patient with generalized lymphadenopathy and systemic B symptoms (persistent fever, night sweats). Lymph node fragments were submitted to Hematopathology Department. Histologic evaluation revealed a lymphoproliferative disorder with a polymorphic cellular composition, rich in T cells with a T follicular helper (TFH) immunophenotype, and scattered Hodgkin-like large B cells. The differential diagnosis included TFH-rich classic Hodgkin lymphoma (cHL) and nodal TFH lymphoma, however subsequent clonality and mutational analysis favored the former. This case highlights the diagnostic challenge posed by prominent TFH marker expression in the background of cHL.

Biopsy Fixation Details

The biopsy specimen was fixed in 10% neutral buffered formalin prior to processing.

Frozen Tissue Available

No frozen tissue is available.

Details of Microscopic Findings

Histologically, the lymph node architecture was effaced by a diffuse and vaguely nodular mixed inflammatory infiltrate. The infiltrate consisted of abundant histiocytes forming aggregates, small lymphocytes without significant atypia

and few eosinophils. Many scattered large cells with Hodgkin-like morphology, including binucleated and multinucleated forms, were identified.

Immunophenotype

Large Hodgkin-like cells were CD30+ and to a lesser extent CD15+ with diffuse, weak to strong PAX5 expression, partial weak to strong CD79a expression and were negative for CD20. Few CD30+ large-to-medium-sized cells tended to cluster loosely.

The small lymphocytic population was predominantly of T-cell lineage without loss of pan-T-cell makers (CD3, CD2, CD5, CD7). CD4+ T cells predominated and formed rosettes around large cells. Surprisingly, TFH marker expression was frequent (ICOS ~70%, PD-1 ~60%, CXCL13 ~20%, BCL6 ~20%, CD10 <5%), whereas only rare, poorly formed PD1+ rosettes surrounding large cells were found.

Nodular aggregates of small CD20+ B cells, associated with expanded follicular dendritic meshworks (CD21+, CD23+) were observed.

In situ hybridization for EBV demonstrated positivity restricted to small bystander nuclei.

Cytogenetics

No cytogenetic studies were performed.

Molecular Studies

BIOMED-2 PCR clonality analysis showed no evidence of monoclonal TRG (VJa/VJβ) or IGH (FR1-FR3) rearrangements.

NGS analysis (Euroclonality-NDC panel) identified an ATM c.580 A>G variant with a frequency of 48% (VUS, possibly germline); no mutations in RHOA, IDH2, TET2, DNMT3A genes and no monoclonal TR or IG rearrangements were detected.

Proposed Diagnosis

The absence of panT cell marker loss, T cell clonality and TFH-lymphoma associated mutations favored the diagnosis of mixed cellularity cHL.

Interesting Feature(s)

This case illustrates the overlapping histology between TFH-rich cHL and TFH lymphoma with secondary Hodgkin-like cells. TFH marker expression in the background T cell population was more extensive than typically observed in cHL and included both sensitive and specific TFH markers. The expansion of FDC meshworks and the presence of rare TFH rosettes could further contribute to diagnostic confusion with angioimmunoblastic-type TFH lymphoma. Clonality and mutational analysis were critical in supporting the diagnosis of cHL in the context of these unusual findings.

Panel Diagnosis: classic Hodgkin lymphoma mc with background T-FH rich

EA4HP26-LYWS-212

A CD30 negative nodular sclerosis classic Hodgkin lymphoma

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Hospices Civils de Lyon, Pathology, Oullins - Pierre Bénite, France

Case Description

A 30-year-old female patient with no significant medical history presented with a recent onset of cervical lymphadenopathy. CT scan revealed cervical and mediastinal lymphadenopathy, the largest measuring 32 x 22 mm. The patient had lost weight (-4 kg) but had no fever, night sweats or asthenia. There were no signs of biological inflammation. The complete blood count showed only lymphopenia (L = $0.77 \times 10^9/L$). Infectious disease workup was negative. PET scan confirmed the presence of a cervical and mediastinal polyadenopathy with a maximum SUV of 11.6. A cervical lymph node biopsy was performed.

Biopsy Fixation Details

Neutral buffered formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

One lymph node measuring 23 x 19 x 15 was analyzed. The lymph node had a nodular growth pattern, with nodules surrounded by fibrosis. Within the nodules, the cell population was polymorphic, with small lymphocytes, histiocytes, plasma cells, a few eosinophils and large cells with irregularly shaped nuclei and vesicular chromatin, containing one or more prominent nucleoli. These large cells were sometimes binucleated or multinucleated. They were reminiscent of Hodgkin and Reed Sternberg (HRS) cells. These cells tended to form aggregates, mixed with numerous histiocytes, with small foci of necrosis in the center of these aggregates. Small lymphocytes, plasma cells and eosinophils were present at the periphery of these areas.

Immunophenotype

The HRS cells did not express CD30. This marker highlighted a few cells around the HRS cells, which may correspond to activated lymphoid cells. The HRS cells expressed CD15. They expressed PAX5, with a lower intensity than the accompanying small B lymphocytes. With the anti-CD20 and CD19 antibodies, there was partial and often incomplete membrane staining of a few HRS cells. Regarding the others markers B, they did not express CD79a, OCT2, BOB1 or PU1. They expressed GATA3 and MUM1. They did not express CD45, CD10, BCL6 or MEF2B. EBV-encoded small RNA (EBER) was negative. The anti-PDL antibody is difficult to interpret due to significant staining of histiocytes mixed with HRS cells; nevertheless, these cells seemed to be positive with this antibody. The small lymphocyte population consisted predominantly of small CD3+ T lymphocytes compared to small CD20+ B lymphocytes, with a large majority of CD4+ cells compared to CD8+ cells.

Cytogenetics

No

Molecular Studies

There was no immunoglobulin nor T-cell receptor gene rearrangement (BIOMED-2). Next generation sequencing did not show any mutations with the panel used.

Proposed Diagnosis

Nodular sclerosis classic Hodgkin lymphoma CD30 negative with partial expression of B markers. The diagnosis of 'grey zone' lymphoma is not retained due to insufficient expression of programme B, especially in this extra-mediastinal location.

Interesting Feature(s)

CD30 negativity in classical Hodgkin lymphoma

Panel Diagnosis: classic Hodgkin lymphoma (EBV-negative) with unusual phenotype (CD30 essentially negative), nodular sclerosis

EA4HP26-LYWS-214**Peripheral T-cell lymphoma NOS, TFH phenotypewith Hodgkin and Reed-Sternberg-like cells**

PhD/MD student Sandra Sanchez, Dr. Francisco J. De La Pinta, Dr. Rebeca Manso, PhD/MD Socorro M. Rodriguez

Fundación Jiménez Díaz, Hematopathology, Madrid, Spain

Case Description

We present the case of a 77-year-old man with a history of multiple myeloma, renal cancer, high blood pressure, dyslipidemia, cholecystopancreatitis and basal cell carcinoma of the skin. In May 2019, he showed an enlarged left external iliac lymphadenopathy (32 x 16 mm, AP x T) and a core needle biopsy showed a granulomatous lymphadenitis. In November 2025, the lymph node had increased in size (41 x 27 mm AP x T). The patient has shown no systemic nodal involvement and the bone marrow has been negative for lymphoma.

Biopsy Fixation Details

Formalin-fixed paraffin embedded tissue.

Frozen Tissue Available

No.

Details of Microscopic Findings

A lymph node excisional biopsy revealed effacement of the normal architecture, thickening of the capsule and involvement of the periganglionic adipose tissue by a heterogeneous infiltrate, composed predominantly by small-to-medium-sized lymphocytes arranged around cells with Hodgkin and Reed-Sternberg-like morphology. The pattern was slightly nodular. Abundant multinucleated giant cells.

Immunophenotype

The small cells showed positivity for CD3, Bcl-2, CD4, CD5, CD7, PD1, ICOS, and TCRB and negativity for CD10, CXCL-13, TCRG, CD8, CD20, CD30, Bcl-6, CD15, CD23, and CD79a. Lambda light chain restriction was identified and mild expansion of the dendritic cell network (CD23+) was seen. Large cells showed: CD30+, CD15+, Bcl-2+, weak PAX-5+, CD20-, CD79-, Bcl-6-, CD10-, CD23-, CD3-, CD4-, CD5-, CD7-, CD8-, PD1-, ICOS-, CXCL13-, and MNDA-. T lymphocytes (CD3+, CD4+, PD1+, ICOS+) formed rosettes around these large cells. Flow cytometry studies showed a monoclonal T cells population (8%).

Cytogenetics

No.

Molecular Studies

TCR gamma gene clonal peaks were observed by conventional PCR. Targeted NGS panel showed pathogenic variants in TET2 (VAF 12%). This mutation was retrospectively found in the FNAC from May 2019 as well.

Proposed Diagnosis

Peripheral T-cell lymphoma NOS, TFH phenotype

Interesting Feature(s)

This case is unique because it belongs to a particularly difficult group of TFHL in which the presence of accompanying HRS-like cells raises the differential diagnosis with CHL. Most diagnostic challenges were posed by the presence of HRS cells in a polymorphic background, a feature of both TFHL and CHL. Firstly, HRS and HRS-like cells share a similar immunophenotype. HRS-like cells were intensively positive for BCL-2 in this case, a feature not previously described in HRS-like cells of TFHLs. On the contrary, HRS cells positive for BCL-2 have been described in CHL, a finding classically considered an independent adverse prognostic factor that may contribute to the failure of primary therapy and the inability to save CHL patients after relapse.

According to the literature, one of the most useful clues to avoid a potential misdiagnosis of CHL in a case of TFHL with HRS-like cells lies in the careful evaluation of CD30 expression. Our case showed heterogeneous/variable CD30-positivity in small to medium-sized cells. On the contrary, it has been described that reactive small T-lymphocytes in CHL are CD30 negative (or very weakly positive), which starkly contrasts with the strong positivity of HRS cells.

Clonality studies are very useful, TFHL instances have detectable clonal TCR gene rearrangements (75% in the literature), which are rarely present in CHL. Our case showed TCR gamma clonality by PCR. In this case, NGS did not help us in the diagnosis, TET2-gene mutation itself is not specific for TFHL, and CHIP mutations including TET2 have also been described in CHL. Interestingly, the patient has shown a stable clinical course since 2019 with a localized lymphadenopathy.

Panel Diagnosis: Possible peripheral T-FH lymphoma with HRS-like cells

Epstein-Barr virus (EBV) associated lymphoid proliferation with overlapping features of classic Hodgkin lymphoma and chronic EBV-positive lymphoid cell proliferation

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Case Description

- 67-year-old man, known case of diabetes mellitus, presented with a progressive painless neck swelling for 8 months.
- No B symptoms were present.
- 18F-FDG PET/NCCT scan revealed:
 - Hypermetabolic discrete and conglomerated right cervical lymph nodes with bulky level II nodal mass measuring 8.4 x 4.4 cm with SUVmax 15.07
 - Low grade metabolism in few marrow lesions
- Complete blood count (CBC) – Within normal limits
- Peripheral blood EBV DNA titre – 12842 copies/mL
- Bone marrow aspirate and biopsy - Uninvolved
- Right cervical lymph node excisional biopsy was received.

Biopsy Fixation Details

- 10% buffered formalin

Frozen Tissue Available

- Not available

Details of Microscopic Findings

- Effaced nodal architecture by admixed population of small lymphoid cells, plasma cells, histiocytoid cells, occasional eosinophils, and few large cells.
- No classic Reed-Sternberg (RS)-like cells seen.
- No granulomas seen.
- No necrosis seen.

Immunophenotype

- CD20 and Pax-5 positive nodular aggregates of B-lymphoid cells with compact CD21 positive FDC meshwork are identified; these nodular aggregates of B-lymphoid cells are positive for IgD; while negative for CD10 (possibly representing primary follicles)
- Interfollicular zone:
 - Highlighted by CD3 with retained expression of CD2 and CD7
 - CD4>>CD8
 - Few cells are positive for TBX21; while Gata3 staining is insignificant
 - Few cells are positive for ICOS and PD-1
 - Negative for CD10
- Large atypical cells:
 - Positive for CD30, MUM1, OCT2, BOB1, TBX21, Bcl-6, EBV-LMP1 and EBER

- Weakly positive for Pax-5
- Few cells show weak positivity for CD15
- Very occasional cell is positive for CD20
- Negative for CD79a, STAT6, CD200, IgD, and GATA3
- Positive for PD-L1 (Ventana SP263 clone) (along with some of the smaller lymphoid cells)

Cytogenetics

- Not available

Molecular Studies

- Not available

Proposed Diagnosis

•EBV-associated atypical lymphoid cell proliferation with overlapping features of classic Hodgkin lymphoma and chronic EBV-positive lymphoid cell proliferation, favour classic Hodgkin lymphoma.

Interesting Feature(s)

- The case showed significant immunohistomorphological overlap between classic Hodgkin lymphoma and chronic EBV-positive lymphoid cell proliferation.
 - Absence of classic RS cells and absence of staining for Gata3, STAT6, and CD200 in the large cells were suggestive of chronic EBV-positive lymphoid cell proliferation.
 - However, progressive, multiple lymph nodes, bulky nodal mass, normal CBC findings (no leukocytosis/lymphopenia/lymphocytosis), inconsistency in B-cell markers expression, no significant reactive B-lymphoid cell proliferation, and distorted architecture of the follicles were not compatible with chronic EBV-positive lymphoid cell proliferation, and more consistent with classic Hodgkin lymphoma.
 - High titres of EBV DNA were neither compatible with chronic EBV nor CHL
- In keeping with the clinical history (especially the size of the mass and progressive nature), the diagnosis of classic Hodgkin lymphoma was favoured.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV positive) mixed cellularity

EA4HP26-LYWS-236

Classic Hodgkin Lymphoma with Cytotoxic Phenotype

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Case Description

- 47-year-old man, first evaluated at an outside centre for inguinal swelling in 2015, diagnosed as classic Hodgkin lymphoma, and was treated with 5# ABVD.
- After a disease-free interval of 8.5 years, he presented with a new onset cervical swelling in November 2024.
- The patient then received 6# CHOPE (last date 30 April 2025). Interim PET scan post 4# revealed complete metabolic response. The patient was referred to our centre for bone marrow transplant.
- Cervical lymph node excisional biopsy (November 2024) was received for review.

Biopsy Fixation Details

- 10% buffered formalin

Frozen Tissue Available

- Not available

Details of Microscopic Findings

- Effaced architecture by large expansile nodules separated by fibrous bands.
- The nodules are composed of admixed population of small lymphoid cells, few eosinophils and singly scattered atypical large (mono, bi and multinucleated) cells.

Immunophenotype

- The atypical large cells are positive for CD30 and CD15.
- These cells are negative for LCA, CD20, CD19, Pax5, OCT2, BOB1, EBV-LMP1, EBER (by bright field in situ hybridization), CD200, GATA3, STAT6, TBX21 (T-bet), CD56, CD57, and ALK1.
- On additional evaluation, the large cells are positive for PD-L1 (Ventana SP263 clone), MUM1, granzyme B, TIA1, and perforin A, weakly positive for CD25, and some cells show weak positivity for EMA.
- CD3 marks the preponderant small T-lymphoid cells, which show marked preponderance for CD8 positive cells over CD4 positive cells, and retained expression of CD2 and CD7. Many of the small lymphoid cells are positive for TIA1; while these cells are negative for granzyme B and GATA3.

Cytogenetics

- Not available

Molecular Studies

- Not available

Proposed Diagnosis

- Classic Hodgkin lymphoma (CHL), nodular sclerosis subtype, with cytotoxic microenvironment and phenotype

Interesting Feature(s)

- The histomorphological features reminiscent of classic Hodgkin lymphoma coupled with the immunophenotype of the large cells (negative pan-B and T cell markers and positivity for cytotoxic markers) and the cytotoxic T-cell predominant cellular microenvironment

Panel Diagnosis: Classic Hodgkin Lymphoma with unusual phenotype (PAX5-, cytotoxic molecules)

EA4HP26-LYWS-237

Classic Hodgkin Lymphoma with Unusual Histomorphology

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Case Description

- 18-year-old man presented with cough for 1 month and significant weight loss.
- 18F FDG PET/CECT scan revealed Stage IVXB disease with
 - Heterogeneously enhancing bulky soft tissue nodal mass with necrotic components within in the superior and anterior mediastinum, measuring 11.8 x 9.2 x 9.6 cm with SUVmax 18.26.
 - Hypermetabolic discrete mediastinal prevascular nodes largest measuring 1.2 x 1.3 cm with SUVmax 10.18.
 - Hypermetabolic marrow lesions (SUVmax 11.51 in L1 vertebra)
 - Mild bilateral pleural effusion.

- Moderate pericardial effusion.
- Mediastinal mass core biopsy was received.
- The patient was planned for 6# of ABVD.
- Interim PET scan after completion of 3 cycles of ABVD showed partial response with residual marrow lesion in the right humerus (Deauville's score 5).
- After completion of remaining 3 cycles of AVD (bleomycin was omitted in view of drop in pulmonary function), the patient presented with a new onset painful right axillary swelling; no B symptoms were present.
- 18F FDG PET/NCCT revealed
 - New onset discrete right supraclavicular and axillary nodes, largest axillary node measuring 2.2cm with SUVmax 14.0
 - Significant increase in metabolism of marrow lesion involving right humerus
 - No significant interval change in size of non-metabolically active anterior mediastinal nodal mass
- Right axillary lymph node was excised.

Biopsy Fixation Details

- 10% buffered formalin

Frozen Tissue Available

- Not available

Details of Microscopic Findings

1.Mediastinal mass core biopsy:

Cores of hyalinised fibrocollagenous tissue with patchy areas of cellularity composed of admixed population of small lymphoid cells admixed with singly scattered atypical large pleomorphic cells.

2. Right axillary lymph node excisional biopsy:

Effaced lymph nodal architecture by polymorphous population of small lymphoid cells, eosinophils, few histiocytes, and numerous atypical small to intermediate-sized mononuclear cells and scattered large (mono, bi, and multinucleated) cells. Foci of necrosis are noted.

Immunophenotype

1.Mediastinal mass core biopsy:

•The atypical large cells are positive for CD30, MUM1, PAX-5; weakly positive for CD15, GATA3, STAT-6, CD200; few cells show weak positivity for OCT2.

•These cells are negative for CD19, CD20, BOB1, and EBER (by bright field in situ hybridization).

•CD3 marks the admixed T-lymphoid cells, most of these cells are negative for GATA3.

2. Right axillary lymph node excisional biopsy:

•The atypical large and intermediate-sized cells are positive for PAX5 (weak), CD30, CD15, MUM1, CD200, and GATA3; some of these cells are positive for OCT2, STAT6, and TBX21 (Tbet); few cells are positive for BOB1; an occasional large cell showed weak expression of p63 protein.

•The atypical cells are negative for EBV-LMP1.

•CD3 marks the admixed T-lymphoid cells.

•On bright field in situ hybridization, few EBER-positive cells are noted, which appear to be bystander small lymphoid cells, while the atypical CD30-positive cells are negative.

Cytogenetics

- Not available

Molecular Studies

- Not available

Proposed Diagnosis

- Classic Hodgkin lymphoma

Interesting Feature(s)

•The presence of numerous CD30 positive small to intermediate sized cells along with typical large RS-like cells with co-positivity for CD15 and STAT6 with dim positivity for PAX5 and absence of CD20.

•Absence of EBV in the neoplastic cells (both in the pretreatment and relapsed tissue) with presence of EBV-

positive bystander (CD30-negative) small lymphoid cells (highlighted by dual procedure of IHC and ISH for CD30 and EBER).

Panel Diagnosis: Relapse of classic Hodgkin lymphoma associated with EBV+ lymphoproliferative disorder

EA4HP26-LYWS-242

An unusual case of classic Hodgkin lymphoma expressing cytotoxic molecules

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Case Description

A 44-year-old male patient presented with cervical lymphadenopathy. Thirty-two months earlier the diagnosis of classic Hodgkin lymphoma (cHL) was made based on a core needle biopsy of a mediastinal lymph node. Due to suspicion of recurrence, an enlarged lymph node was excised and submitted for consultation.

Biopsy Fixation Details

4% buffered formaldehyde

Frozen Tissue Available

No

Details of Microscopic Findings

The architecture of the enlarged lymph node was effaced due to an infiltrate rich in macrophages that also contained irregular nodular aggregates of small lymphoid cells with hyperchromatic nuclei reminiscent of residual mantle zones. Residual germinal centers were rarely present. Several atypical large cells exhibiting features of Hodgkin- and Reed-Sternberg (HRS) cells were located either at the borders of the nodular lymphoid aggregates or between macrophages.

Immunophenotype

The HRS cells consistently expressed CD30, weakly PAX5, the Epstein-Barr virus (EBV)-encoded latent membrane protein-1, as well as partially CD15. In addition, all HRS-cells strongly expressed perforin, and mostly also granzyme B, while TIA1 was partially and weakly expressed. There was no expression of CD20, CD3, CD2, CD5, ALK/CD246 and CD45.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Classic Hodgkin lymphoma (EBV-positive), mixed cellularity with expression of cytotoxic molecules

Interesting Feature(s)

This case represents a cHL showing an unusual expression of three cytotoxic molecules (Perforin, Granzyme B and to a lesser extent TIA1). This phenomenon has been reported in single studies, but its precise occurrence is currently unknown (PMID: 21859738, PMID: 1695451, PMID: 10807764). The cases reported up to now have shown an association with an EBV-infection in 39% but in contrast to our case, a constant absence of PAX5. These PAX5-negative cHL cases expressing cytotoxic molecules have been reported to show a poorer prognosis compared to cHL without cytotoxic molecules (PMID: 21859738, PMID: 16954517). In contrast to these PAX5-negative cHL cases, which require additional studies to clarify the differential diagnosis with ALK-negative anaplastic large cell lymphoma,

the present case does not pose diagnostic difficulties as the remaining immunophenotype is consistent with the diagnosis of cHL.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-positive), with unusual phenotype (expression of cytotoxic molecules), mixed cellularity

EA4HP26-LYWS-254

Lymphocyte-rich classic Hodgkin lymphoma

Dr. Haipeng Shao, Dr. Christopher Ryder

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Case Description

The patient was a 68 year-old male who presented with left sided neck mass, and no other symptoms. PET/CT showed multiple enlarged FDG avid lymph nodes in the left neck up to 2.1 cm in diameter and maximum SUV of 8.4, and no other metabolically active lymph nodes or metabolically active lesions in the liver or spleen. After the diagnosis, the patient was treated with 4 cycles of ABVD (Adriamycin- bleomycin- vinblastine- dacarbazine). PET scans showed signs of recurrence. The patient received treatment with 3 cycles of salvage regimen ICE (Ifosfamide- carboplatin-etoposide) with PET scan showing complete response after 2 cycles. He underwent BEAM (BCNU/carmustine-etoposide-cytarabine-melphalan) conditioning followed by autologous stem cell transplant with post-transplant maintenance with brentuximab (anti-CD30 ADC). Recent PET/CT showed features of progression and a left cervical lymph node was performed. Lymphoma team was planning on treatment with nivolumab.

Biopsy Fixation Details

10% formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

The lymph node architecture is effaced by diffuse lymphoid infiltrate. There are small numbers of scattered large atypical lymphoid cells admixed in a background of small mature lymphocytes and few scattered epithelioid histiocytes. The large atypical lymphoid cells include Reed-Sternberg cells and cells resembling lymphocyte-predominant (LP) cells. Eosinophils and neutrophils are absent.

Immunophenotype

By immunohistochemical staining, the large atypical lymphoid cells are positive for CD30, CD15 (subset), MUM1 (strong), PAX-5 (weak) and OCT2 (weak), and negative for CD20. The CD3 positive T cells form rosettes around HRS cells, and are negative for PD1.

Corresponding flow cytometry is negative for a clonal B cell or abnormal T cell population.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Lymphocyte-rich classic Hodgkin lymphoma

Interesting Feature(s)

This case is a diffuse pattern lymphocyte-rich classic Hodgkin lymphoma. The HRS cells show classic phenotype with expression of CD30, CD15 (subset), MUM1 and weak PAX5, and negative CD20. Of note, the presence of some large atypical lymphoid cells resembling LP cells and resetting of T-cells around HRS cells raise the differential diagnosis of nodular lymphocyte predominant Hodgkin lymphoma. The absence of complete B-cell program in the

HRS cells, such as CD20 expression, absence of strong expression of OCT2 and absence of PD1 positive T follicular helper cells rule out nodular lymphocyte predominant Hodgkin lymphoma.

Panel Diagnosis: classic Hodgkin lymphoma with rich B cell background (small B cell lymphoma associated not proven)

EA4HP26-LYWS-255

An unusual variant of classic Hodgkin lymphoma

Dr. Elsa Poullot¹, Dr. Sarah Bellal², Dr. Radu Pirlog¹, Cyrielle Robe¹, Dr. Josette Brière¹, Dr. Aline Clavert³, Prof. Emmanuèle Lechapt-Zalcman¹, Prof. Philippe Gaulard¹

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Case Description

A 40-year-old woman with no significant medical history is examined in August 2025 for mediastinal, left cervical and supraclavicular adenopathies. She shows no B symptoms. A surgical biopsy of the supraclavicular lymph node is performed (slides submitted). ABVD treatment is administered, with complete response to 2 cycles, followed by AVD (ongoing).

Biopsy Fixation Details

Formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

The biopsy involves a muscular and adipose tissue infiltrated by cohesive sheets of large atypical and pleomorphic neoplastic cells. Some areas are rich in immunoblasts-like cells, others in clear large cells, while some of them contain cells morphologically compatible with Hodgkin and Reed Sternberg cells (HRS). Mummified cells and small foci of necrosis are observed. In some areas, neoplastic cells are admixed with numerous eosinophils and neutrophils, small reactive lymphocytes are virtually absent. Focal nodular sclerosis is present.

Immunophenotype

The lymphoid cells are CD30+ (diffuse and strong expression), CD15+, MUM1+, CD4+ (diffuse, weak), and shows only partial and weak expression of PAX5, with high proliferation index (Ki67). Cells are negative for : ALK1, CD20, CD79a, OCT2, BOB1, CD19, EBER probes, CD2, CD3, CD5, CD7, CD43, TIA1, granzyme B, perforine, LEF1, EMA, P63.

Cytogenetics

FISH : No *DUSP22* rearrangement.

Molecular Studies

Monoclonal Ig rearrangement, TCR polyclonality.

Targeted Gene Sequencing (TGS) : mutations in *DNMT3A* (VAF 35.9%), *GNA13* (3 variants 19.6% to 27.9%), *SOCS1* (7 variants VAF 15.8% to 31.1%), *STAT6* (VAF 20.3%) , *TP53* (VAF 39.8%), *TNFAIP3* (VAF 20.1%).

Proposed Diagnosis

Syncytial variant of nodular sclerosis classic Hodgkin lymphoma (CHL).

Interesting Feature(s)

- Rare histological variant with sheets of neoplastic cells without typical HRS morphology, and misleading features with other lymphomas, especially anaplastic large cell lymphoma, diffuse large B cell lymphoma or mediastinal grey zone lymphoma.

- Unusual phenotype with only weak and partial expression of PAX5, diffuse expression of CD4.
- Value of molecular studies (clonality and TDS) in the differential diagnosis of this tumor-cell rich subtype of CHL.

Panel Diagnosis: Classic Hodgkin Lymphoma nodular sclerosis syncytial pattern

EA4HP26-LYWS-262

Unusual case of classic Hodgkin lymphoma with features of lymphocyte-depleted subtype.

Jessica Anderson-Calleja, Dr. Lauren Smith

University of Michigan, Pathology/Hematopathology, Ann Arbor, USA

Case Description

74-year-old woman with enlarged inguinal lymph node and hypercalcemia.

Biopsy Fixation Details

Formalin-fixed.

Frozen Tissue Available

n/a

Details of Microscopic Findings

The lymph node is effaced by an infiltrate of variably-sized, pleomorphic Hodgkin/Reed-Sternberg (HRS) cells in large sheets/clusters. The large atypical cells include some that are multinucleated with horseshoe-shaped nuclei. There are areas of necrosis. Few admixed small lymphocytes and histiocytes are present. There are no well-formed hyaline bands or nodules.

Immunophenotype

The HRS cells are positive for CD30, CD15, CD4 (subset), and PAX5 (weak/variable). The cells are negative for CD2, CD3, CD5, CD7, CD20, and EBER (rare bystander lymphocytes positive).

Cytogenetics

FISH studies for ALK, TP63, TBL1XR1/TP63, and DUSP22-IRF4 are negative.

Molecular Studies

T-cell clonality studies were negative (TCR gamma and TCR beta). A clonal IGK light chain gene rearrangement was detected. IGH was negative.

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-depleted.

Interesting Feature(s)

This case meets many of the described features of the reticular subtype of lymphocyte-depleted classic Hodgkin lymphoma (CHL). Even in a busy academic consult practice, this subtype is exceedingly rare. It also has overlapping morphologic/immunophenotypic features with anaplastic large cell lymphoma (ALCL), including CD4 expression.

Panel Diagnosis: Classic Hodgkin Lymphoma lymphocyte depleted

Classic Hodgkin Lymphoma with Aberrant Expression of T-Cell Markers

Dr. Youssef Khafateh, Dr. Nives Zimmermann

University of Cincinnati, Department of Pathology and Laboratory Medicine, Cincinnati, USA

Case Description

The patient is a 22-year-old female with history of migraine headache and gallstones who presented with nonpainful mass on the left side of her neck. On imaging, she was found to have extensive cervical and mediastinal lymphadenopathy. The patient then underwent an excisional biopsy of left neck lymph node.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Histologic sections show a lymph node with complete effacement of the normal architecture by an atypical cellular infiltrate. The infiltrate is composed mostly of small lymphocytes, with some plasma cells, histiocytes, and eosinophils, in addition to frequent large, atypical cells. The large cells have prominent eosinophilic nucleoli with occasional binucleation (some classic Reed-Sternberg like cells seen). Some of the large cells appear as lacunar cells.

Immunophenotype

Immunostains demonstrate that atypical large cells are positive for CD30, PAX-5 (weak), and CD15, while they are essentially negative for CD20, OCT2, and CD79a. Some of these large cells demonstrate staining for many T-cell markers (including CD3, CD4, CD5, and CD7) as well as focal staining for CD45. Those large cells are negative for ALK and EBER. CD4 and CD8 highlight predominantly CD4+ T-cells in the background. Controls demonstrated appropriate staining.

Cytogenetics

Not performed.

Molecular Studies

B-cell gene rearrangements and T-cell gene rearrangements are performed. B-cell gene rearrangements showed a clonal immunoglobulin heavy chain (IgH) gene rearrangement, while T-cell gene rearrangements (both beta and gamma) are negative.

Proposed Diagnosis

Classic Hodgkin Lymphoma with aberrant expression of T-cell markers.

Interesting Feature(s)

The interesting feature of this case is the expression of several T-cell markers in classic Hodgkin lymphoma. This feature occurs only in a small subset of classic Hodgkin lymphoma cases and can present a diagnostic challenge and might have prognostic significance.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-negative) with unusual phenotype (T-cell antigen expression), nodular sclerosis

Post-treatment Classic Hodgkin lymphoma with TIA-1(+) cells

Dr. Tran Nguyen¹, Dr. Jeffrey Welsh², **Dr. Elena Fenu**¹

¹ Duke University Medical Center, Pathology, Durham, USA; ² Lexington Medical Center, Pathology, West Columbia, USA

Case Description

71-year-old male patient with a past medical history of Hodgkin's lymphoma, stage IV (4/7/2025) status post chemotherapy presents for an oncology follow-up in 10/2025.

Initially, the patient reported a 3-month history of night sweats, chills, and unintentional weight loss since 12/2024, then right neck lymphadenopathy in 03/2025, which progressively enlarged. Subsequent CT chest abdomen and pelvis showed extensive bulky lymphadenopathy in the neck, liver lesions, and osteolytic lesions in the right pubic symphysis and right iliac.

Initial right cervical lymph node biopsy showed classic Hodgkin lymphoma, nodular sclerosis subtype. Following chemotherapy (nivolumab-AVD [doxorubicin, vinblastine, dacarbazine]), a PET scan (7/8/2025) showed significant improvement with residual low-grade hypermetabolic left supraclavicular adenopathy. However, repeat PET scan after cycle 6 (10/2025) showed enlarging left supraclavicular and paratracheal lymph nodes. He underwent left supraclavicular lymph node excisional biopsy in 10/2025.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Sections show an infiltrate of large pleomorphic cells with prominent nucleoli and occasional bi- and multi-nucleation, in a background of mixed inflammatory cells. Atypical cells focally form large clusters.

Immunophenotype

Large atypical cells are positive for CD30, CD15 (major subset), MUM1, PAX5 (weak), TIA-1, CD21, and BCL6 (subset). They are negative for CD45, CD20, CD19, CD79a, CD3, ALK1, CD43, OCT2, BOB-1, EBER CISH, PanCK, and pan-melanoma.

CD20 stains rare small lymphocytes. CD3 stains most background small lymphocytes which show retained CD2, CD5, and CD7 expression. PD-1 stains rare scattered small cells. Granzyme B stains granulocytes. Flow cytometry showed predominantly CD4+ T-cells (CD3 99% and CD4 81.3%) without antigen loss or atypical co-expression.

Cytogenetics

Not performed

Molecular Studies

B-cell clonality (IgH): Positive

T-cell clonality (TCR Gamma): Negative

T-cell clonality (TCR Beta): Indeterminate

Proposed Diagnosis

CD30+ lymphoproliferative neoplasm, favor Classic Hodgkin lymphoma.

Interesting Feature(s)

Neoplastic cells show syncytial morphology and some aberrant antigen expression (CD21 and TIA-1), however, the overall phenotype (CD30+, CD15+, MUM1+, PAX5+, CD45-) favors residual/recurrent Classic Hodgkin lymphoma. The clonality studies and initial partial treatment response also favors the diagnosis. Expression of CD21 and TIA-1 may rarely be seen in Classic Hodgkin lymphoma.

This patient is considered to have refractory disease, which is associated with a poor prognosis and limited standard options. The oncologist plans to switch to a different chemotherapy backbone, such as a brentuximab vedotin (BV)-based or gemcitabine-based regimen.

Panel Diagnosis: Classic Hodgkin Lymphoma

EA4HP26-LYWS-282

#282 Lymphadenopathy with a history of AITL

Dr. Alexander M. Craig, Dr. Christine Heisen, Dr. Yaso Natkunam, Dr. Joshua Menke

Stanford Medicine, Hematopathology, Palo Alto, USA

Case Description

A 68-year-old female with reported history of T-follicular-helper cell lymphoma, angioimmunoblastic type (AITL) presented with lymphadenopathy. Patient underwent periaortic LN biopsy. Flow cytometry showed normal lymphocytes, 89% of events (14% of which were B-cells).

Biopsy Fixation Details

4 cores, formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Cores of lymphoid tissue with scattered large, atypical cells characterized by irregular nuclear contours, prominent nucleoli, and occasional multinucleation in a mixed lymphohistiocytic background. Hints of germinal centers are visible, but no clear nodal architecture is apparent. Atypical cells are scattered in the interstitium as well as localized to within residual B-cell nodules. High-endothelial venules are not prominent.

Immunophenotype

Large atypical cells are positive for CD20 (also highlights dense background small mature B-lymphocytes) and weakly positive for PAX5 and Bcl-2. Bcl-6 mostly highlights histiocytes. CD3 and CD5 highlight T-lymphocytes - predominantly positive for CD4 - ringing the atypical cells. Subsets of atypical cells are positive for CD15 and CD45 is equivocal in larger cells. They are negative for CD10 and other markers tested. CD21 demonstrates few intact follicular dendritic cell meshworks, highlighting mantle zone B-lymphocytes, and Bcl-6 demonstrates no/few residual germinal centers. Large atypical cells are variably/weakly positive for OCT2, CD79a (strongly highlights background B-lymphocytes), and MUM1, predominantly negative for MEF2B. Proliferative index by Ki-67 is approximately 10-20% overall, and highlights larger cells. PD1 and EBER ISH are negative.

Cytogenetics

None

Molecular Studies

T-cell clonality negative. B-cell clonality positive for IGH and IGK. NGS: DNMT3A E733* 13%, PPM1D R552* 13%, IRF8 R375Q (VUS) 46%, RRAGC V264I (VUS) 47%

Proposed Diagnosis

Proposed Diagnosis: CD30+ large B-lymphoproliferative disorder, most consistent with lymphocyte-rich classic Hodgkin lymphoma.

Interesting Feature(s)

Interestingly, the original case of AITL was also reviewed and a secondary EBV negative B-cell lymphoma was identified, with variably sized cells highlighted by CD20 and PAX5. As secondary B-cell proliferations can be seen in AITL – though usually these are EBV positive – and may resemble Hodgkin/Reed-Sternberg cells, it is extremely challenging to distinguish those cases from classic Hodgkin lymphoma, especially on a limited core biopsy.

As with other differential diagnoses involving Hodgkin lymphomas, the degree of B-cell marker expression is a useful discriminatory feature. LR-cHL exhibits more robust expression of B-cell markers when compared to other cHL subtypes (Nam-Cha et al, Mod Pathol 2009). This case shows robust staining for PAX5 and CD79a, with variable staining of CD20 and OCT2, most in keeping with LR-cHL overall.

The intense T-cell background in this case could be further characterized by flow cytometric immunophenotyping with TRBC1 as a proxy for clonality; however, flow cytometry in this case was negative and was not run with TRBC1, and thus neither supports nor rules out AITL or CHL. Fortunately, T-cell gene rearrangement studies by NGS were performed, and these were negative, providing no evidence for a clonal T-cell process and further arguing against AITL. (The previous case diagnosed as AITL showed TCR-gamma, IGH, and IGK clonal rearrangements).

Approximately 4 months after the biopsy just discussed, a biopsy of a retroperitoneal lymph node was performed. T-cell clonality studies by NGS were negative, and mutations in DNMT3A and PPM1D were identified at similar VAF to the above.

Panel Diagnosis: Lymphocyte-Rich classic Hodgkin Lymphoma

EA4HP26-LYWS-287

Classic Hodgkin lymphoma with concomitant low grade B cell lymphoma and follicular helper T cell proliferation

Dr. Xiaohui Zhang^{1,2}, Dr. Fnu Monika³, Dr. Ling Zhang³

¹ James A Haley Veterans' Hospital, Pathology and Laboratory Services, Tampa, USA; ² University of South Florida College of Medicine, Pathology and Cell Biology, Tampa, USA; ³ H. Lee Moffitt Cancer Center, Pathology, Tampa, USA

Case Description

79-year-old male has a history of liver transplant in 20 years ago and cutaneous T cell lymphoma and melanoma. He noticed an enlarged cervical lymph node. PET/CT scan showed generalized lymphadenopathy, splenomegaly up to 16cm, and multiple hypermetabolic foci throughout colon and right pleural effusion. Left supraclavicular lymph node was 4.7 x 3 cm with SUV of 16.4. Flow cytometry analysis on fine needle aspirate sample detected clonal B cell population. An excisional biopsy of left supraclavicular lymph node was performed.

Biopsy Fixation Details

The lymph node was fixed in 10% formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

The lymph node architecture was effaced with atypical lymphoid proliferation. The lymphoid cells were composed of aggregates of small lymphoid cells, scattered large lymphoid cells resembling Reed-Sternberg (RS) cells, and clusters of histiocytes. Rare scattered eosinophils were present.

Immunophenotype

Immunohistochemical stains were performed. There were aggregates of T cells and B cells. The T cells were predominantly TFH cells positive for CD3, CD5, CD7, CD4, PD-1, ICOS, BCL6, and CXCL13. CD4:CD8 ratio was 3~4:1. CD21 stain showed expanded follicular dendritic cell meshworks. EBER ISH was negative. The B cells were positive for CD20, PAX5, and negative for CD5, CD10, BCL1, and SOX11. The scattered large lymphoid (RS-like) cells were positive for CD30, CD15, MUM1, PAX5 (weak), and CD20 (variable). EBER ISH was negative. Flow cytometry analysis was performed on the excisional biopsy sample. A clonal B cell population was detected with the below phenotype: CD19+, CD20+, CD5-, CD10-, lambda light chain+, and kappa light chain -.

Cytogenetics

N/A

Molecular Studies

Molecular studies for B cell gene rearrangement and T cell gene rearrangement were performed, which were positive for clonal IgH gene rearrangements, and negative for clonal TCR gene rearrangements.

Proposed Diagnosis

Classic Hodgkin lymphoma with concomitant low grade B cell lymphoma and follicular helper T cell proliferation.

Interesting Feature(s)

This is a diagnostically challenging case in a remote posttransplant setting, that has features of classic Hodgkin lymphoma (cHL) in a background of clonal B cell proliferation, follicular helper T (TFH) cell proliferation, and clusters of histiocytes. The RS-like cells can be seen in many B cell and T cell lymphomas including marginal zone lymphoma and nodal TFH lymphoma. On the other hand, reactive TFH cell proliferation can also be seen in marginal zone lymphoma (Egan C, et al. Am J Surg Pathol. 2020. 44(5):657) and classic Hodgkin lymphoma (Petronilho S., et al. Am J Surg Pathol. 2025 49(3):273). The characteristic background milieu of classic Hodgkin lymphoma can be obscured by the concomitant B cell and reactive TFH cell proliferation. In this case, the diagnosis of cHL required differentiation from marginal zone lymphoma and nodal TFH lymphoma with RS-like cells. The diagnosis based on morphology, immunophenotype, and molecular studies was particularly challenging initially and became more evident only after treatment eliminated background clonal B cell population.

Panel Diagnosis: Classic Hodgkin Lymphoma with TFH and B cell enriched background

EA4HP26-LYWS-302

A wolf in sheep's clothing: multiply refractory lymphocyte-rich classic Hodgkin lymphoma

Dr. Miekhan Stonhill, Dr. Sam Sadigh

Mass General Brigham, Pathology, Boston, USA

Case Description

A 25-year-old man presented to primary care clinic with a painless lump in the right neck. Imaging showed enlarged, FDG-avid right cervical and supraclavicular nodes. He underwent core needle biopsy, which did not yield a definitive diagnosis, followed by excisional biopsy, which was initially interpreted as non-diagnostic at an outside institution. The patient's lymphadenopathy persisted, and he developed increasing fatigue and night sweats. Given his worsening clinical symptoms, he was referred for a second excisional biopsy which was diagnostic of lymphoma. After diagnosis, he was treated with 6 cycles of ABVD, with initial significant response but with end-of-treatment PET showing recurrent right cervical lymphadenopathy. Core and excisional biopsy showed relapsed disease. He then underwent salvage treatment with Pembro-GVD, with persistent disease at end of treatment, confirmed by excisional biopsy (reviewed below). He was then treated with bendamustine, followed by autologous stem cell transplant and maintenance brentuximab and remains in remission (two subsequent biopsies of FDG-avid nodes showing reactive findings).

Biopsy Fixation Details

Formalin, B+

Frozen Tissue Available

No

Details of Microscopic Findings

H&E sections show markedly enlarged lymph node profiles with architectural effacement by a nodular proliferation of predominantly small lymphocytes with few eosinophils and plasma cells. Singly scattered large cells were present

within the nodules and exhibited irregular to lobated nuclei with vesicular chromatin and distinct nucleoli. A few background germinal centers were seen.

Immunophenotype

Large cells were positive for CD30, PAX5 (weak), MUM1, BCL6 (subset), BOB1, and CD15 (subset), and negative for CD20, CD79a, CD10, OCT2, and EBER. The background lymphoid cells consisted of CD20+, IgD+ B cells in nodules and CD3+ T cells predominantly outside follicles. Nodules were associated with CD21+ follicular dendritic cell meshworks. Flow cytometry showed no clonal B-cell or unusual T-cell population.

Cytogenetics

46,XY[cp16]

Molecular Studies

N/A

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte-rich subtype (LR-CHL), nodular pattern

Interesting Feature(s)

This case showed unusual architecture and significant morphologic overlap with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), with Hodgkin/Reed-Sternberg cells being relatively rare and located within B cell-rich nodules, which were associated with expanded follicular dendritic cell meshworks and contained few residual germinal centers. However, the HRS cells in this case showed a typical immunophenotype, confirming a diagnosis of classic Hodgkin lymphoma.

LR-CHL can be difficult to diagnose, often requiring multiple biopsies, as in this case; this patient underwent eight lymph node biopsies in total, requiring paired core and excisional biopsies on two occasions.

Prediction of clinical outcomes in Hodgkin lymphoma is difficult; gene expression profiling and whole-slide analysis have both been used on a research basis, with decreased non-neoplastic B cells and abundance of histiocytes both being associated with a worse prognosis (PMID: 20220182, 32381573). LR-CHL typically presents at a lower stage than other subtypes and rarely involves the mediastinum, leading to an excellent prognosis. However, despite its relatively innocuous histologic features, this case was notably aggressive, with primary refractory disease requiring multiple lines of salvage treatment and autologous stem cell transplant.

Panel Diagnosis: Classic Hodgkin Lymphoma Lymphocyte-Rich with an NLPHL growth pattern

EA4HP26-LYWS-303

EBV(+) lymphoma with Reed-Sternberg cells and numerous atypical T-cells with a T-follicular helper immunophenotype, favor nodular sclerosis-type classic Hodgkin lymphoma.

Dr. Tran B. Nguyen¹, Dr. Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

¹ Duke University School of Medicine, Department of Pathology, Durham, USA; ² Duke Cancer Institute, Durham, USA

Case Description

The patient is a 24-year-old woman with no significant past medical history who was found to have significant mediastinal lymphadenopathy during evaluation following a positive COVID-19 test. Imaging studies demonstrated diffuse mediastinal lymphadenopathy, and a subsequent positron emission tomography scan revealed bulky hypermetabolic mediastinal, supraclavicular, and cervical lymphadenopathy. The patient underwent an excisional cervical lymph node biopsy. Following the final diagnosis, she received ABVD chemotherapy.

Biopsy Fixation Details

Sections of the lymph node were fixed in formalin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Sections reveal fragments of lymph node with diffuse architectural effacement. Normal lymph node components are largely replaced by a dense infiltrate of small mature lymphocytes with mild nuclear atypia, interspersed with abundant Reed-Sternberg cells and rare eosinophils and plasma cells. The infiltrate is subdivided into discrete nodules surrounded by dense bands of sclerotic collagen in some foci.

Immunophenotype

Reed-Sternberg cells are positive for CD30, CD15, PAX-5(weakly+), Fascin, MUM-1, BCL-6, EBER in-situ hybridization; and negative for CD3, CD5, CD7, CD20, CD45, CD79a, BOB-1, and ALK-1. CD3 highlights numerous background T cells, which are positive for CD2, CD4, CD5, CD7, CD8(subset), CXCL13, ICOS, BCL-6; and negative for CD10 and PD-1.

Flow cytometry: No abnormal T-cell population identified.

Cytogenetics

Not performed

Molecular Studies

T-cell receptor gene rearrangement studies fail to demonstrate a clonal T-cell population.

Proposed Diagnosis

EBV(+) lymphoma with Reed-Sternberg cells and numerous atypical T-cells with a T-follicular helper immunophenotype, favor nodular sclerosis-type classic Hodgkin lymphoma.

Interesting Feature(s)

- The lymph node shows extensive architectural effacement by numerous EBV-positive, CD30-positive Reed-Sternberg cells; however, the typical mixed inflammatory background of classical Hodgkin lymphoma is largely replaced by a population of small mature lymphocytes with mild cytologic atypia, rather than prominent eosinophils and plasma cells.
- Immunohistochemical studies demonstrate that the background lymphoid population is composed predominantly of CD4-positive T cells expressing TFH-associated markers (BCL6, ICOS, and CXCL13), with absence of CD10 and PD-1 expression. This immunophenotypic profile is atypical for conventional classical Hodgkin lymphoma and raises consideration of alternative diagnostic entities.
- The combination of abundant EBV-positive Reed-Sternberg-like cells and a TFH-enriched T-cell background raises the differential diagnosis of a T-cell lymphoma with Hodgkin-like features, a well-described but non-WHO-defined category encompassing subsets of angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, NOS. Despite the atypical morphologic and immunophenotypic features, T-cell receptor gene rearrangement studies fail to demonstrate a clonal T-cell population, arguing against an underlying T-cell lymphoma and supporting classification as classical Hodgkin lymphoma.

Panel Diagnosis: Classic Hodgkin Lymphoma with TFH enriched background

Lymphoma with morphologic findings in favor of a diagnosis of lymphocyte-depleted classic Hodgkin lymphoma and clonality studies identifying clonal TRG rearrangement

PhD/MD Yen-Chun Liu

St. Jude Children's Research Hospital, Department of Pathology, Memphis, USA

Case Description

A 15-year-old boy presented with ~20 lb weight loss over 2-3 months along with night sweat, generalized weakness and fatigue. Imaging showed widespread FDG avid disease including multi-station supra and infra diaphragmatic lymphadenopathy, massive splenomegaly with focal areas of abnormal uptake, peritoneal implants and axial/appendicular skeletal lesions. An excisional biopsy of the left supraclavicular lymph node showed findings of a malignant lymphoma, favor lymphocyte-depleted classic Hodgkin lymphoma (submitted). With stage IVB disease, the patient received non-protocol treatment based on HLHR13 consisting of AEPA/COP-Dac. He completed the therapy in January 2024 and has been off therapy with no evidence of disease.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections of lymph node show effacement of architecture by an infiltrate composed of numerous histiocytes, lymphocytes, scattered large pleomorphic cells resembling Hodgkin/ Reed Sternberg cells (HRS) and variants. Rare eosinophils are noted. There is fine fibrosis throughout the node and evidence of capsular fibrosis.

Immunophenotype

The large atypical cells are positive for CD15 (focal, Golgi pattern), CD30, MUM1, PAX5 (weak), negative for CD20, CD79a, CD3, CD2, CD5 and CD7. BCL6 is focally positive in some of the HRS cells. EBER ISH is focally positive in scattered small cells, but negative in the HRS-like cells. The immunostains highlight clustering of the abnormal cells in vague nodules. Background T-cells lack cytological atypia and have no significant immunophenotypic aberrancies such as loss of pan T-cell antigens including CD2, CD5 and CD7. There are more CD8-positive T cells than CD4-positive T cells in the background. There is no significant increase in TFH cells based on the BCL6, CXCL13, ICOS, PD1, and CD10 stains.

Cytogenetics

N/A

Molecular Studies

Immunoglobulin gene rearrangement studies (IGH and IGK) detected clonal rearrangement.

T-cell receptor gene rearrangement studies (TRG) detected clonal rearrangement.

Target panel mutation analysis demonstrated alterations with low allele frequencies (AF): *TNFAIP3* (NM_006290.4: c.477T>A; p.Tyr159Ter); AF 3%

Proposed Diagnosis

Malignant lymphoma, favor lymphocyte-depleted classic Hodgkin lymphoma

Interesting Feature(s)

The current lesion in a pediatric patient demonstrates widespread disease and morphologic findings in favor of the rare lymphocyte-depleted subtype of classic Hodgkin lymphoma, with increased fibrosis and a background composed of lymphocytes and numerous histiocytes. The presence of clonal IG rearrangement and genetic alterations with low allele frequencies detected by targeted panel mutation analysis also supports such diagnosis. Although the presence of a prominent clonal TRG rearrangement is unusual for a diagnosis of Hodgkin lymphoma and raises concern for a

T-cell neoplasm, the lack of significant cytologic atypia or immunophenotypic aberrancies in the background T cells does not substantiate a diagnosis of T-cell lymphoma. The background T-cells in the current lesion are enriched in CD8-positive T cells and do not show significantly increased TFH cells. Of note, the patient's germline sample sent for panels covering cancer predisposition and inborn errors of immunity/primary immunodeficiency did not reveal an apparent pathogenic/likely pathogenic variant; only variants of uncertain significance in *BARD1*, *CFB* and *CFTR* were identified.

Panel Diagnosis: Classic Hodgkin Lymphoma lymphocyte-depleted with T cell clone

EA4HP26-LYWS-317

Lymphocyte-Rich Classic Hodgkin Lymphoma: The Subtype That Whispers

Gianfranco E. Umeres Francia, Barina Aqil

Northwestern University Feinberg School of Medicine, Department of Pathology, Chicago, USA

Case Description

A 45-year-old female without significant past medical history presented with fatigue, night sweats, and a painless right cervical lymph node that had been slowly enlarging over three months. She denied weight loss, pruritus, or recent infections. Physical examination revealed a single, mobile, 2.5 cm lymph node without hepatosplenomegaly. Initial laboratory studies were unremarkable: normal CBC, mildly elevated ESR, LDH within reference range. HIV and EBV serologies were negative. The referring clinician suspected a reactive process but requested an excisional biopsy due to persistent symptoms.

Biopsy Fixation Details

The biopsy was fixed in 10% neutral buffered formalin and interpreted at an outside institution as "Nodular lymphocyte-predominant B-cell lymphoma". The patient was referred to our institution for a second opinion.

Details of Microscopic Findings

At our institution, review of the lymph node showed effacement of architecture by an atypical nodular infiltrate composed of numerous small lymphocytes and few scattered large cells, located both within and outside the nodules. These large cells had irregular nuclear contours, vesicular chromatin, prominent macro-nucleoli, and abundant amphophilic cytoplasm. Some mummified, binucleated, and multinucleated cells were seen. Focal eccentric residual follicles with reactive germinal centers were also noted.

Immunophenotype

By immunohistochemistry, the large atypical cells were positive for PAX5 (weak-moderate), CD20 (subset), OCT2, MUM1, CD30, CD15 (small subset), BCL6 (weak), BCL2 (weak), PD-L1 and negative for CD45 RNA, BOB1, CD10, BCL1, CD79a, CD19, LMP1 and ALK1. EBER-ISH was additionally performed, which was positive in the large cells. CD3 and CD5 demonstrated intermixed T-cells forming rosettes around the large cells. CD23 highlighted follicular dendritic cell meshworks in association with the nodular infiltrate. The residual germinal centers were positive for CD10, BCL6, and negative for BCL2. PD-1 showed increased positive cells rosetting around the large cells. IgD highlighted increased positive cells within the nodules. Flow cytometric immunophenotyping revealed a polytypic B-cell population and a T-cell population without immunophenotypic abnormality based on the markers assayed. No monotypic T-cell population was detected based on TRBC1 expression.

Proposed Diagnosis

Overall, the diagnosis was consistent with lymphocyte-rich classic Hodgkin Lymphoma (CHL-LR).

Interesting Feature(s)

CHL-LR remains one of the most frequently misclassified lymphomas due to its deceptive architecture and immunophenotype. Despite its nodular, B-cell-rich architecture that closely resembles NLPHL, CHL-LR retains classic Hodgkin biology, most notably strong PD-L1 expression on HRS cells, a feature absent in NLPHL and diagnostically powerful in ambiguous cases. The microenvironment adds another layer of complexity, characterized by CD3+/PD-1+ T-cell rosetting around HRS, a feature reminiscent of NLPHL. Flow cytometry frequently fails because HRS cells are sparse and fragile, a pitfall worth emphasizing as clinicians often over-rely on this technique. Finally, TRBC1 clonality assessment is an effective tool to confirm the polyclonal nature of the T-cell background and exclude T-cell lymphomas. Together, these features transform even a classic CHL-LR case into a rich teaching opportunity that showcases diagnostic nuance, microenvironmental insight, and the value of contemporary immunophenotypic tools.

Panel Diagnosis: Lymphocyte-rich classic Hodgkin Lymphoma

EA4HP26-LYWS-320

Classic Hodgkin lymphoma preceded by a lymphoproliferative disorder featuring Hodgkin/Reed-Sternberg-like cells.

Prof. Luisa Lorenzi^{1,2}, Dr. Flavia Melotti², Dr. Marco A. Cocchi¹, Dr. Giulio E. Mandelli², Dr. Mattia Facchetti², Dr. Iacopo Ghini², M.Sc./M.A. Silvia Lonardi^{1,2}, M.Sc./M.A. Emma Albertini^{1,2}, M.Sc./M.A. Martina Benedetti², Dr. Matteo Magni¹, Dr. Alessandro Re³

¹ University of Brescia, Pathology Section, Brescia, Italy; ² ASST Spedali Civili di Brescia, Pathology Unit, Brescia, Italy; ³ ASST Spedali Civili di Brescia, Hematology Unit, Brescia, Italy

Case Description

In May 2022, a 76-year-old woman presented with a 3.5 cm left intraparotid mass that underwent FNAC and surgical resection. Histologically, that lesion was deemed reactive with preserved architecture and scattered CD20+ CD30+ Reed-Sternberg-like cells. The case was shared with international experts, confirming the diagnosis. The patient received no therapy. Small adenopathies with focal metabolic tracer hyperaccumulation appeared from October 2023; she remained asymptomatic until April 2025 (36 months from diagnosis). CT showed persistent laterocervical and mediastinal lymph nodes, prompting a new biopsy (submitted). She achieved metabolic complete remission after 3 cycles of Brentuximab-AVD chemotherapy.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

The lymph node exhibited effaced architecture with a scant B-cell component and an expanded paracortex featuring multiple nodules rich in epithelioid histiocytes, occasionally forming vaguely granulomatous clusters intermixed with numerous small T lymphocytes. Within these nodules—and sometimes outside—large, mono- or multinucleated cells with prominent nucleoli were evident. Some showed a mummified appearance; others were extremely large and pleomorphic.

Immunophenotype

Large atypical cells showed intense positivity for CD30, MUM1, and CD20 (the latter dimly in a small fraction); PAX5 expression varied from strong to weak. CD15 displayed Golgi-dot-like reactivity in some atypical cells, while CD45 was genuinely negative in most. OCT2 was strongly positive, BOB1 mainly negative, and EBV/EBER negative.

Cytogenetics

not performed

Molecular Studies

Double stain for CD30 and RNAscope for Ig light chains revealed a discrete number of CD30+ atypical cells positive for the transcript of the Ig kappa chain.

Proposed Diagnosis

Classic Hodgkin lymphoma, mixed cellularity variant, with partially retained B-cell program

Interesting Feature(s)

The most striking feature of this case is the prior lymphoproliferative disorder with HRS-like cells that preceded overt Hodgkin lymphoma by 36 months. At the time of the initial biopsy, Ig light-chain transcript expression supported a reactive, non-neoplastic process. However, the same finding was evident in the overt lymphoma occurring 36 months later. We therefore performed a retrospective study in our single-center and observed that preservation of the B-cell program that included Ig light-chain expression was detectable (by double stain CD30 & IgLCRNAscope) in about 4% of classic Hodgkin lymphomas.

Panel Diagnosis: Classic Hodgkin Lymphoma with unusual phenotype (B cell markers)

EA4HP26-LYWS-337

Classic Hodgkin lymphoma with T follicular helper rich background or TFH lymphoma

Prof. Sridhar Epari², Prof. Tanuja Shet¹, Dr. Rutvij Khedkar¹

¹ Tata Memorial Hospital, Pathology, Mumbai, India; ² ACTREC, Pathology, Mumbai, Germany

Case Description-58 year old male patient

- Was being evaluated for tingling numbness in both the upper limbs since one month in May 2024
- MRI spine showed few ill-defined variable sized STIR hyperintense signal in B/L pelvic bones, Largest 4.8 x 3.8 cm, Cervical Degenerative disc bulge and Few subcm sized paratracheal, subcarinal nodes.
- Underwent a PET scan:
- FDG avid left level III, IV, V LN (Largest 1.9 x 3.3 cm, SUV 8.3)
- FDG avid left level axillary LN (Largest 1.5 x 1.3 cm, SUV 8)
- Retrocrural, Pre-aortic, Para-aortic, B/L common iliac, external iliac 2.3 x 3.6 cm (SUV = 13.7)
- Mild splenomegaly
- Diffuse uptake in visualized skeletal system

Left supraclavicular node was biopsied

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

No

Details of Microscopic Findings

- Grossly nodes measured 2,1X1 cm cut surface was whitish
- On Histology Lymph nodes show effaced architecture by an admixed population of small lymphoid cells, few histiocytoid cells and atypical large (mononuclear) cells.
- The mononuclear cells were more centroblastic immunoblastic and Hodgkin like with pale eosinophilic to amphophilic cytoplasm.
- The background was lymphocyte rich with very scattered eosinophils. Back small cells were intermediate sized (large than usual reactive cells) and showed occasional mitosis.

Immunophenotype-Positive stains in the large atypical lymphoid cells:

CD30, GATA3, weakly positive for Pax-5; while these large cells.

Negative in the large atypical lymphoid cells: CD20.

\-Positive stains in the small lymphoid cells:

CD3, CD4 and CD7; many of these cells are also positive for GATA3, ICOS and PD1. BCL6 is weakly positive. CD21 marks residual foci of follicular dendritic cell meshwork.

Cytogenetics

nil

Molecular Studies

-Clonality testing by EuroClonality/BIOMED-2 guidelines revealed no T-cell clonal population

Proposed Diagnosis

Classic Hodgkin lymphoma with T follicular helper rich background

Interesting Feature(s)-In classic Hodgkin lymphoma, the immune environment is rich in CD4+ Tregs.

-This entity represents a Classic Hodgkin lymphoma with an unusual reactive microenvironment rich in Tfh(T follicular helper)-cells.

-A close differential was TFH lymphoma but due to lack of clonality diagnosis of CHL was made.

-It appears inspite of this unqiue background patient has good response

Panel Diagnosis: Classic Hodgkin Lymphoma with TFH and B cell enriched background

EA4HP26-LYWS-343

Classic Hodgkin lymphoma, with aberrant expression of T- cell markers.

PhD/MD Natalia Papaleo^{1,2}, Ricard Onieva Carbajo^{1,2}, PhD/MD Carmen Blazquez Maña¹

¹ *Parc tauli university hospital, Pathology, Barcelona, Spain;* ² *Universitat Autònoma de Barcelona, Barcelona, Spain*

Case Description

A 18-year-old woman with a history of congenital deafness, was referred for evaluation of axilar lymphadenopathy of one month's duration. She reported no fever, night sweats, or weight loss at presentation. Routine laboratory workup was unremarkable.

A PET/CT scan revealed an anterior mediastinal adenopathic conglomerate surrounding the mediastinal structures measuring 57 × 85 mm (SUVmax of 12.6 g/ml). In addition, supra-diaphragmatic hypermetabolic lymphadenopathy, a hypermetabolic spleen measuring 25 mm (SUVmax 6.9 g/ml) and bone marrow involvement were observed.

A cervical lymph node biopsy confirmed Classic Hodgkin lymphoma, with aberrant expression of T- cell markers.

The patient received ABVD therapy, achieving complete remission.

Biopsy Fixation Details

4% buffered formaldehyde.

Frozen Tissue Available

None

Details of Microscopic Findings

The lymph node section showed effaced architecture, replaced by an atypical lymphoid proliferation. The atypical cells were large, with abundant clear cytoplasm, large nuclei with prominent nucleoli, and some bilobed Reed–Sternberg–like morphologies forming syncytia in some areas. They were accompanied by histiocytes, small lymphocytes, polymorphonuclear cells, and eosinophils, and are embedded in a fibrotic stroma.

Immunophenotype

The neoplastic cells showed weak positivity for PAX-5, focal CD79a, CD30, CD15, MUM-1 and GATA3; and were negative for OCT-2, CD20, CD45, EMA, EBER, CD23, CD56, Granzyme B, PD-1 and ALK. Aberrant expression of

T-lineage markers, including CD3 and CD4, was also observed. Rosettes with CD5 and CD7 T-cells surround the neoplastic cells were present.

Cytogenetics

None

Molecular Studies

PCR analysis showed polyclonal TCR- β and TCR- γ rearrangements, as well as a polyclonal IgH pattern. Next-generation sequencing results are pending.

Proposed Diagnosis

Classic Hodgkin lymphoma with aberrant expression of T-cell markers

Interesting Feature(s)

Hodgkin lymphoma (HL) is a well-defined clinico-pathologic entity originating from germinal or post-germinal center B-cells, although Hodgkin and Reed–Sternberg (HRS) cells rarely express B-cell markers.

Aberrant expression of T-cell lineage markers in HL is uncommon, occurring in approximately 5% of cases (Girish Venkataram, Blood, 2013). However, it is believed that less than 1% of HL cases originate from a genuine T-cell lineage. One proposed mechanism is that silencing of B-cell markers can lead to the activation of genes inappropriate for the lineage, contributing to this aberrant immunophenotype (Tankov et al., Modern Pathology, 2005).

In the differential diagnosis, certain T-cell lymphomas such as ALK-negative anaplastic large cell lymphoma, nodal T-follicular helper cell lymphoma and peripheral T-cell lymphoma, not otherwise specified, should be considered. They may contain reactive immunoblasts or clonally expanded large B-cells that are CD30 positive and mimic Hodgkin and HRS cells.

The transcription factor GATA3, a T-cell marker, is frequently overexpressed in HL, with the syncytial variant demonstrating the highest rate of positivity (Brie Kezlarian, Applied Immunohistochemistry, 2019).

Panel Diagnosis: Classic Hodgkin Lymphoma

EA4HP26-LYWS-353

CD30 positive lymphoma consistent with Classical Hodgkin lymphoma with syncytial growth pattern, extensive necrosis, aberrant expression of T cell markers and LCA

Biljana Grčar Kuzmanov¹, Gorana Gasljevic^{2,1}, Dora Panna¹

¹ Institute of Oncology Ljubljana, Ljubljana, Slovenia; ² Medical Faculty Maribor, Maribor, Maribor, Slovenia

Case Description

42-yrs-old male, otherwise healthy

Presented with painful lump on the neck which he noticed for the first time in November 2025 and night sweatings; denied other B-symptoms

Clinical examination: 4cm lymph node on the right lower aspect of the neck, slightly fluctuating, no other palpable peripheral lymph nodes, no organomegaly

Lab at admission: Leu 13.13 109/L, Hb 129 g/L, Plt 370 x109/L, LDH 2.51 ukat/L (<4.13), CRP 36.3 mg/L (<5)

HIV, HBs, HBc, Hbe, HCV all negative

Rtg PC: 6 cm large pathological density of the left paramediastinum (probable lymph node conglomerate) + right neck

PET CT ongoing

FNAC: suspicious for cHL. Fistula formation after FNAC.

Excision of the right neck LN together with skin and subcutaneous tissue

Biopsy Fixation Details

10% buffered formalin overnight

Frozen Tissue Available

Yes

Details of Microscopic Findings Numerous neoplastic cells in sheets with extensive necrosis; lymph node, skeletal muscle, subcutaneous and skin infiltration

Syncytia of neoplastic cells, majority of them are mononuclear, medium to large sized. There are some admixed RS cells and lacunar cells

Fibrosis hard to estimate because of extensive infiltration of subcutaneous tissue with reactive changes and mechanical damage of the tissue, in LN is absent

Immunophenotype

Positive for: CD30, PaX5 (dim), MUM-1, PD-L1, focally for CD3, CD5, LCA, CD20 (only rare cells, weakly), CD15 rare cells

Negative for: EBV-ISH, ALK, CD19, CD10, bcl-6, bcl-2, EMA, CD4

Cytogenetics

NA

Molecular Studies

PCR Biomed 2 monoclonal B, polyclonal T

Proposed Diagnosis

CD30 positive lymphoma consistent with Classical Hodgkin lymphoma with syncytial growth pattern, extensive necrosis, aberrant expression of T cell markers and LCA

Interesting Feature(s)

Syncytia of neoplastic cells with extensive necrosis, majority of them are mononuclear, medium to large sized – probably representing NS cHL, syncytial variant. Morphology could be misleading in smaller biopsies. DLBCL and GZL were excluded since B-cell program is not preserved. ALK+ALCL was excluded by ALK negative IHC. ALK-ALCL would show more extensive LCA positive reaction and is only rarely PAX-5 positive due to the extra copies of PAX5. As well, PCR Biomed2 showed presence of monoclonal B and polyclonal T cells in the specimen. Besides, clinical context with mediastinal mass and supraclavicular LN, points toward the diagnosis of cHL.

Aberrant expression of T cell markers: well described in the literature but rarely present, could induce diagnostic pitfalls toward ALCL or other types of PTCLs. Points toward more aggressive clinical behaviour with shorter PFS and OS.

Hodgkin/Reed–Sternberg (HRS) cells are typically CD45 (LCA) negative. Abberant expression of LCA in cHL is exceptional. Could induce differential diagnostic confusion with peripheral T-cell lymphoma, ALCL, DLBCL, GZL.

Extensive infiltration of skin and subcutaneous tissue by cHL with fistulation, mimicking scrofuloderma is extremely rare

Cutaneous involvement by cHL is an extraordinarily rare phenomenon in the current era, usually in the setting of systemic cHL with secondary skin dissemination

Panel Diagnosis: Classic Hodgkin Lymphoma with syncytial pattern

Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL)

Dr. Neha Sharma¹, Dr. Sridhar Epari¹, Dr. Vishesha Adhvaryu¹, Dr. Sachin Punatar¹, Dr. Navin Khattri¹, Dr. Tanuja Shet²

¹ Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai, India; ² Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India

Case Description

21-year-old immunocompetent man presented with on and off fever and generalized weakness for one year.

- On examination, right supraclavicular and bilateral axillary lymph nodes were palpable; hepatosplenomegaly was present.

1) 18F-FDG PET/CECT revealed generalised lymphadenopathy (largest was mediastinal hilar node measuring 4.9cm; SUVmax 11.36) with splenic involvement, and hypermetabolic liver and marrow lesions.

- Right supraclavicular lymph node core biopsy was received.

2) Completed 6 cycles of R-CHOP

Post 6# R-CHOP 18F-FDG PET/CECT scan

No significant change in metabolism of cervical, axillary, mediastinal, abdominal nodes.

However, clinically the patient was completely asymptomatic and was reviewed after 3 weeks with repeat PET-scan

3) On repeat 18F-FDG PET-CT scan revealed:

- Significant increase in size and metabolism of cervical, bilateral axillary, mediastinum, abdomen, pelvic and inguinal nodes. Overall scan finding suggest disease progression

Clinically, patient was asymptomatic but in view of PET progression, biopsy was planned.

Biopsy Fixation Details

- 10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

1) Tissue cores showed sheets of atypical intermediate to large sized lymphoid cells in sheets with frequent apoptotic bodies. Geographic necrosis was noted.

2) Abdominal node biopsy showed hyalinisation and patchy areas of cellularity, composed of small lymphocytes, plasma cells and few admixed large atypical cells.

3) Right axillary node excision showed effaced architecture by polymorphous population of lymphoid cells composed of small lymphocytes, numerous neutrophils, few plasma cells, and scattered atypical large (predominantly mononuclear) cells.

Immunophenotype

1) • The atypical cells were positive for CD19, MUM1, CD30, CD38 and EBER-ISH.

- Few of these cells showed a weak staining for CD20.

- These cells were negative for PAX5, CD79a, ALK1, BCL6, CD10, and LMO2.

- myc protein labeling index was approximately 40-50% and MIB1 labeling index was approximately 60-70% in the highest proliferating areas.

2) • The large cells were positive for MUM1, CD30; and few cells showed weak staining for CD19 and STAT6.

- These cells were negative for CD20, CD15, GATA3, PAX5, CD138, and EBER-ISH.

3) • The atypical large cells were positive for CD30, MUM1 and weakly positive for PAX5

- Some of the cells showed positivity for STAT6, OCT2 and CD20

- These cells were negative for CD79a, BOB1, CD19, EBV-LMP1 and EBER-ISH
- CD3 marked the preponderant admixed small T-lymphoid cells.

Cytogenetics

No

Molecular Studies

No

Proposed Diagnosis

1. Possibility of CD20-negative EBV-positive diffuse large B cell lymphoma, not otherwise specified (NOS) was considered.
2. The immunohistomorphological features are of a classic Hodgkin lymphoma-like immunophenotype.
A repeat biopsy was advised.
3. Large B-cell lymphoma with classic Hodgkin lymphoma phenotype.

Interesting Feature(s) Young male presented with systemic EBV positive CD20-negative B-lymphoid cell proliferation with no tell-tale clinical evidence of immunodeficiency

Rapid evolution into classic Hodgkin lymphoma-like large B-cell lymphoma

Challenges

- What is the primary presentation - is it systemic reactive B-lymphoid cell proliferation with high MIB-1/Ki-67 labeling , or EBV-positive DLBCL, NOS?
- CD20 negativity in EBV-positive B-lymphoid proliferation: is it a marker of neoplasia or part of the spectrum of EBV induced changes
- How to explain the lack of EBV in the relapse/subsequent evolution, i.e. EBV negativity in the subsequent CHL-like lymphoma with preceding EBV-positive B-lymphoid cell proliferation

Panel Diagnosis: not classified

EA4HP26-LYWS-356

Nodular lymphocytic predominant Hodgkin lymphoma in a lymphatic malformation

Dr. Fatima M.A. Khan, Amer Wahed, Andy Nguyen, Hanadi El Achi, Brenda Mai

Mc Govern Medical School, University of Texas Health Science Center Houston, Pathology and Laboratory Medicine, Houston, USA

Case Description

- 15-year-old male presented initially with chronic left shoulder pain and shoulder weakness.
- According to the patient, his symptoms first started after riding an all-terrain vehicle for several hours while at camp and remained unchanged since onset.
- Over the counter pain-killers offered minimal relief.
- On physical examination, a large subcutaneous tender cystic mass was noted midway down the medial scapula border that disappeared with shoulder adduction.
- MRI findings were suggestive of a lymphatic malformation.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

Not performed

Details of Microscopic Findings

- Histologic sections of the tissue show nodules with a predominance of small B cells, T-cells, and histiocytes are present.
- The large atypical cells had pale eosinophilic cytoplasm and folded nuclear membranes; some of the nuclei show multinucleation and a conspicuous nucleoli.
- Large lymphocyte predominant cells (LP cells) were present outside of the nodules and surrounded by small CD4+ cells and histiocytes and were not associated with follicular dendritic cell (FDC) meshworks.
- Necrosis was not present.

Immunophenotype

- The large atypical LP cells expressed CD20, PAX-5, BCL-6, OCT-2, but were negative for MUM-1, CD30 and CD15.
- Evaluation for CD45 and CD43 expression in the atypical cells was challenging due to the significant background of small lymphocytes.
- CD21 and CD23 highlighted the follicular dendritic cell meshwork.
- The follicles contain abundant CD20-positive small B-cells.
- CD3 highlights the T-cell that are present predominantly in the parafollicular areas and co-express CD5 and BCL-2.
- CD138 demonstrate scattered plasma cells which were polyclonal by kappa-ISH and Lambda-ISH.
- The Ki-67 highlighted the large cells; it was difficult to quantify due to the scarcity of the LP cells.
- Cyclin-D1, CD10, EBV-ISH, AE1/AE3, S100 were negative.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Nodular lymphocytic predominant Hodgkin lymphoma, pattern C

Interesting Feature(s)

- Nodular lymphocytic predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) are distinct, but overlapping, types of B-cell lymphomas that can be challenging to differentiate diagnostically.
- Cases with at least one typical nodule are generally classified as THRLBCL-like NLPHL. In this case, the large lymphocyte predominant cells (LP cells) were present outside of the nodules and surrounded by small CD4+ cells and histiocytes and were not associated with follicular dendritic cell (FDC) meshworks, creating a diagnostic challenge.
- It is nearly impossible to distinguish between the two based solely on the appearance of the individual tumor cells; the overall tissue architecture and the composition of the surrounding non-cancerous cells are the most reliable diagnostic features.
- The site of involvement for this case is unusual, NLPHL is usually found in the peripheral lymph nodes; mediastinal involvement is uncommon and it is rare to have it seen as posterior chest wall and mistaken as a lymphatic malformation on imaging.

Panel Diagnosis: Lymphocyte-Rich classic Hodgkin Lymphoma

EBV+ lymphocyte rich classic Hodgkin lymphoma with extensive granulomatous reaction and abundant Tfh T-cells; diagnostic challenges in distinction from nodular lymphocyte predominant Hodgkin lymphoma.

Dr. Saiaditya Badeti, Dr. Christian Salib, Dr. David Gajzer, Dr. Bruce Petersen, Dr. Dalia Abdel-Azim, Dr. Alina Dulau-Florea, Dr. Duffield Amy, **Dr. Shafinaz Hussein**

Mount Sinai Hospital, Icahn School of Medicine, Pathology and Laboratory Medicine, New York, USA

Case Description

76-year-old man with a history of lymphocyte rich classic Hodgkin lymphoma (LRCHL), diagnosed 10 years prior at an outside institution. He was treated with AAVD and achieved complete remission. Approximately 7 years after diagnosis, a PET/CT revealed hypermetabolic diffuse lymphadenopathy. Excisional biopsy of a left axillary lymph node (2.3 x 1.6 cm; SUV 11) revealed EBV(+) CHL. He was treated with pembrolizumab, gemcitabine, vinorelbine and liposomal doxorubicin (P-GVD) achieving remission.

Two years after relapse, PET/CT revealed hypermetabolic left cervical lymphadenopathy (2.2 x 1.6 cm; SUV 13.2). Quantitative PCR detected EBV DNA (40.6 IU/mL). The lymph node was excised.

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

H&E reveals an enlarged lymph node with effaced architecture. There are scattered large, atypical cells with coarse/vesicular chromatin, irregular nuclear contours and variably prominent eosinophilic nucleoli. The background consists of small lymphocytes and numerous epithelioid histiocytes and sarcoid-like non-necrotizing granulomata. Eosinophils are inconspicuous.

Immunophenotype

The large, atypical cells are CD30+ (uniform, strong), CD15+ (subset), PAX5 moderate-weak, OCT2 (uniform, bright), CD20+ (uniform, bright), CD79a+ (weak), MUM1+ (bright), BCL6 equivocal and EMA-. BOB1 appears negative-weak. CD45 appears negative. EBER-ISH is positive in the atypical cells. The background consists of expanded irregular mantle zones (CD23+, IgD+). CD21 highlights expanded/irregular dendritic meshworks associated with follicles. The neoplastic cells are present within abnormal mantle zones and interfollicular areas. The interfollicular zones consist mainly of T cells (CD3+) with a predominance of CD4+ T cells, which form rosettes around the neoplastic B cells. PD1 highlights many T cells including those forming rosettes.

Cytogenetics

N/A.

Molecular Studies

N/A.

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte rich, EBV(+)

Interesting Feature(s)

1. Lymphocyte rich classic Hodgkin lymphoma (LRCHL) is an uncommon variant that shares similar morphologic and immunophenotypic features with nodular lymphocyte predominant Hodgkin / B-cell lymphoma (NLPHL). Both entities exhibit nodules of small mature lymphocytes that contain admixed large atypical cells.

2. This case demonstrates several additional morphologic features that are more often associated with NLPHL, including expanded follicular dendritic cell meshworks underlying the nodules and clusters of epithelioid histiocytes / granulomata surrounding the nodules.
3. Extensive granulomata can obscure the neoplastic HRS cells and lead to diagnostic pitfalls, particularly in small / limited biopsy samples (PMID: 39491628).
4. The Hodgkin/Reed-Sternberg (H/RS) cells of this LRCHL case are identified by their strong and uniform expression of CD30 and MUM-1 and are also positive for EBV; however, the H/RS cells share similarities with the lymphocyte predominant (LP) cells of NLPHL including relatively bright/robust expression of several B cell markers, including OCT2, CD20 and CD79a; localization within B-cell rich nodules; and increased PD1+ T follicular helper cells with rosette formation around the neoplastic cells.
5. The morphologic and immunophenotypic similarities between LRCHL and NLPHL necessitate full immunophenotypic evaluation, and adequate tissue sampling may be required to arrive at the correct diagnosis (PMID: 35987347, 38059511).

Panel Diagnosis: EBV-positive nodular lymphocyte-predominant Hodgkin lymphoma

EA4HP26-LYWS-370

Classic Hodgkin Lymphoma in an immunosuppressed patient with disseminated *Mycobacterium genavense* infection

Dr. Andrea Coetzee, Dr. Shafinaz Hussein, Dr. Alina Dulau-Florea, Dr. Christian Salib, Dr. Amy Duffield

Icahn School of Medicine at Mount Sinai, Department of Pathology, Molecular and Cell-Based Medicine, New York, USA

Case Description

A 32-year-old woman with a 4-year history of sarcoidosis/Löfgren's syndrome and currently treated with anti-TNF therapy presented with persistent fevers and progressive generalized lymphadenopathy (August 2024). Imaging demonstrated extensive lymphadenopathy above and below the diaphragm and inflammatory markers were markedly elevated. An initial infectious workup was negative. Excisional biopsy of left neck lymph node (September 2024) demonstrated necrotizing granulomatous inflammation with acid fast bacilli and no evidence of lymphoma. A bone marrow biopsy was negative, with no mycobacteria detected in the blood or bone marrow. The patient continued to experience B-symptoms with radiologic progression. Repeat excisional biopsy in February 2025 showed classic Hodgkin lymphoma in the setting of extensive necrotizing granulomatous inflammation. Broad range bacterial sequencing performed on the lymph node tissue detected *Mycobacterium genavense*. The patient was diagnosed with disseminated *Mycobacterium genavense* infection and stage IVB Hodgkin lymphoma and treated with nivolumab/doxorubicin/vinblastine/dacarbazine and an antibiotic regimen.

Biopsy Fixation Details

Formalin fixed paraffin embedded tissue.

Frozen Tissue Available

None.

Details of Microscopic Findings

Enlarged lymph nodes demonstrate extensive necrotizing granulomatous inflammation. The limited uninvolved nodal tissue contains a mixed inflammatory infiltrate comprised of small lymphocytes, histiocytes and occasional eosinophils. There are scattered large, atypical cells with abundant cytoplasm, one or more large nuclei, and prominent nucleoli that are morphologically consistent with Hodgkin/Reed-Sternberg cells.

An AFB special stain highlights scattered acid-fast bacilli. A GMS special stain is negative for fungal organisms.

Immunophenotype

The Hodgkin and Reed-Sternberg cells are highlighted by CD30, CD15 (focal), MUM-1 and PAX-5 (weak), but are negative for CD20, CD3 and EBV (EBER-ISH). CD3 highlights frequent background T cells, and CD20 highlights occasional background B cells.

Flow cytometry shows a mildly increased CD4:CD8 ratio (7.3:1) with no evidence of a clonal B-cell population.

Cytogenetics

None.

Molecular Studies

Broad range bacteria PCR-based sequencing detected *Mycobacterium genavense*.

Proposed Diagnosis

Classic Hodgkin lymphoma with concurrent *Mycobacterium genavense* lymphadenitis.

Interesting Feature(s)

This is an unusual case of classic Hodgkin lymphoma (CHL) with concurrent *Mycobacterium genavense* infection, in a patient with a history of anti-TNF therapy and sarcoidosis. Sarcoidosis and CHL may share overlapping clinical features, including B-symptoms, lymphadenopathy, and granulomatous inflammation [PMID: 39859309, PMID: 36584716]. *Mycobacterium genavense* is a rare nontuberculous mycobacterium seen in severely immunosuppressed patients, and typically requires molecular methods for definitive identification. *Mycobacterium genavense* and other mycobacterial infections (leprosy, tuberculosis, *Mycobacterium avium* complex) have rarely been reported in association with CHL [PMID: 35731199]. This association raises the possibility of the altered microenvironment and/or immune dysregulation in mycobacterial infections contributing to the development of lymphoma. Additionally, the development of more sensitive molecular methods may allow for the detection of novel or low-level infectious agents associated with lymphomas.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV-negative), immunodeficiency/immundysregulation with M. genavense infection

EA4HP26-LYWS-382

Stage IV lymphocyte-rich classic Hodgkin lymphoma presents in young female with cardiac and B symptoms.

Dr. Andres G. Madrigal, Dr. Kelly Walker, Prof. Robert Booth, Prof. Paul Romanoski

The University of Toledo, Pathology, Toledo, USA

Case Description

29-year-old female with a history of gastritis and chronic venous insufficiency presented with shortness of breath and heart palpitations on exertion, dizziness, loss of appetite, cough, acid reflux, and night sweats. Reports 17-pound (7.7 kg) weight loss in the past 3 months. Physical exam reveals an ill-appearing pale patient with tachycardia, splenomegaly and lower leg edema. No cervical adenopathy on physical examination.

Vitals: BP 123/73; pulse 129, weight 53.1 kg (117 lb), SpO2 99%.

Laboratory values were notable for significant iron deficiency anemia (RBC $2.9 \times 10^6/\mu\text{L}$, Hgb 7.6 g/dL, HCT 26.4%, MCV 91.0 fL), absolute neutrophilia ($13.1 \times 10^3/\mu\text{L}$), absolute monocytosis ($1.78 \times 10^3/\mu\text{L}$). Platelets were within reference range. Additional laboratory studies include decreased iron (25 ug/dl), TIBC (190 ug/dL), iron saturation (13%), and albumin (2.7 g/dL); increased alkaline phosphatase (157 U/L) and CRP 197.2 mg/L. Serum EBV IgG positive; EBV IgM negative. No abnormal lab results with ANA, RA factor, electrophoresis immunofixation or hemolysis studies. Peripheral blood review noted plasmacytoid lymphocytes. No abnormal findings on peripheral blood flow cytometry studies.

Abdominal ultrasound confirms splenomegaly (20.2 x 17.7 x 9.9 cm) with heterogenous parenchymal echogenicity, concerning for a lymphoproliferative disease. PET/CT identified supraclavicular adenopathy, bulky lymphadenopathy in the mediastinum with a combined maximum diameter of 12.6 cm extending from hilum to hilum with a maximum SUV of 7.0; diffuse spleen enlargement, periportal and periaortic adenopathy. A supraclavicular lymph node biopsy and bone marrow examination performed.

Biopsy Fixation Details

10% Neutral Buffered Formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Sections show lymph node parenchyma with effaced architecture. There are scattered large highly atypical cells with greatly enlarged nuclei and prominent nucleoli. Some of these cells are multinucleated or binucleated with the appearance of classic Reed-Sternberg cells. The tumor cells are dispersed in a background of small, mature lymphocytes. No increase in eosinophils seen.

Immunophenotype

Neoplastic cells express CD30 and CD15 (subset).

Neoplastic cells are negative for CD20, CD45 expression.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Lymphocyte –rich classic Hodgkin lymphoma

Interesting Feature(s)

Young adult female with history of chronic vascular insufficiency presents with cardiac features (shortness of breath and palpitations on exertion), B-symptoms (weight loss, night sweats) and stage IV disease (Ann Arbor classification). Clinically challenging due to non-specific laboratory studies.

Assessment of bone marrow involvement challenging due to patchy distribution of dense bone marrow fibrosis and rare CD30-positive cell. Normal cytogenetics and no mutations detected in the bone marrow specimen (images available upon request).

Panel Diagnosis: Lymphocyte-Rich classic Hodgkin Lymphoma

EA4HP26-LYWS-384

Classic Hodgkin lymphoma with necrotizing granuloma

Dr. Brenda Mai, Dr. Amer Wahed, Dr. Andy Nguyen, Dr. Jacob Armstrong, Dr. Paul Chaiken

University of Texas Health Science Center Houston, Pathology, Houston, USA

Case Description

The patient is a 40 year old male with a past medical history significant for HIV. He presented with a one year history of unintentional weight loss of 40 pounds, fatigue, cough, lower extremity edema, pancytopenia and a decreased CD4 count that did not correlate with viral RNA titers. After ruling out other causes such as histoplasmosis, toxoplasmosis, cryptococcus, tuberculosis, and hepatitis with serologic testing and a lack of response to treatment for presumed community acquired pneumonia and influenza, the clinical team considered a malignant etiology. The patient received PET/CT which showed increased FDG uptake in the bilateral supraclavicular, right axillary,

mediastinal lymph nodes as well as in the spine and pelvis. Shortly after, the patient underwent core biopsy of the right axillary lymph nodes.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

None available

Details of Microscopic Findings

- Diffuse mixed Infiltrate consisting predominantly of histiocytes, small lymphocytes and occasional plasma cells, with scattered large, atypical cells admixed.
- Patchy granulomatous inflammation with focal necrosis.

ImmunophenotypeCD3, CD20, Alk are negative.

CD15, CD30, PAX5, EBER ISH are positive

Concurrent flow cytometry of the bone marrow and right axillary lymph node tissue showed a decreased CD4:CD8 ratio with no other immunophenotypic abnormalities.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

EBV-positive Classic Hodgkin lymphoma, mixed cellularity, with granuloma formation and patchy necrosis

Interesting Feature(s)

- Necrosis in classic Hodgkin lymphoma (CHL) is a rare finding, often seen in advanced stages or specific subtypes like lymphocyte depletion; interestingly, this case was a CHL mixed cellularity subtype
- Necrosis on PET scans can be a negative prognostic factor, indicating more aggressive disease
- The presence of necrosis and granulomas on histology can mimic infections or sarcoidosis, potentially masking the lymphoma
- Necrotic granulomas can be misdiagnosed as infections (tuberculosis, fungal) or sarcoidosis, requiring careful pathological examination

Panel Diagnosis: Classic Hodgkin Lymphoma

EA4HP26-LYWS-385

PRIMARY EXTRANODAL LYMPHOCYTE RICH CLASSICAL HODGKIN LYMPHOMA INVOLVING NASOPHARYNX

Dr. Tugfan Kokturk¹, Dr. Mehmet Ozcan², Dr. Isinsu Kuzu¹

¹ University of Ankara, School of Medicine, Pathology, Ankara, Turkey; ² University of Inonu, Pathology, Malatya, Turkey

Case Description

A 36-year-old male with tonsil enlargement symptoms in 2019 admitted and tonsillectomy was performed resulting the diagnosis of reactive hyperplasia. In December 2024 was evaluated at an outside Otorhinolaryngology clinic due to persistent and progressing symptoms. Endoscopic examination revealed a mass at the nasal root. He reported no additional complaints. His laboratory tests were within normal limits. PET/CT showed a 2.7 × 2.6 × 2.0 cm nodular space-occupying lesion in the nasopharyngeal region with increased FDG uptake (SUVmax: 11.0), with no other pathological activity elsewhere. Nasopharyngeal biopsy was performed at the outside hospital

Biopsy Fixation Details

Buffered formalin

Frozen Tissue Available

no

Details of Microscopic Findings

Curetted tissue fragments from the nasopharynx, were lined by epithelium with underlying organized lymphoid tissue. Follicular organization with identifiable germinal centers were prominent component in the lymphoid tissue. Within the follicles and in the surrounding areas scattered large atypical lymphoid cells were present. These cells were showing mono or multilobated nuclei, prominent nucleoli, and abundant cytoplasm; resemble Reed–Sternberg cells.

Immunophenotype

The described large cells with lobulated nuclei show diffuse strong positivity for CD30 and CD15, while EBV-LMP1 and EBER were negative. These cells are strongly positive for MUM1 and weakly positive with PAX5. CD20, BOB1, OCT2 and BCL6 were negative in the atypical large cells. CD20 and Pax5 revealed well organised B cell follicles and the background is composed of mostly reactive small B cells. CD3 demonstrates T lymphocytes with a normal distribution in follicles and surrounding the atypical large cells in a rosette-like pattern. CD23 shows germinal center areas consistent with a prominent, preserved FDRC network, and in a few foci, scattered FDRCs are observed particularly in B-cell-rich areas, with follicular structures demonstrating surrounding naïve B cells.

Cytogenetics

not performed

Molecular Studies

not performed

Proposed Diagnosis

LYMPHOCYTE-RICH CLASSICAL HODGKIN LYMPHOMA WITH ISOLATED EXTRANODAL NASOPHARYNGEAL INVOLVEMENT

Interesting Feature(s)

This case underscores the clinical and diagnostic significance of lymphocyte-rich classical Hodgkin lymphoma (LRCHL), which accounts for approximately 4–5% of Hodgkin lymphomas, while primary nasopharyngeal involvement remains exceptionally rare. Although LRCHL is classically characterized by peripheral nodal disease, involvement of the Waldeyer's ring is a recognized extranodal/head-and-neck pattern that is encountered more commonly in this subtype compared with other variants. Consistent with this clinical spectrum, our patient presented primarily with long-standing, progressive nasal obstruction in 2019 and diagnosed as reactive. The recent onset of the disease without additional systemic complaints the lesion appeared as an isolated nasopharyngeal mass on PET/CT.

Panel Diagnosis: Lymphocyte-rich classic Hodgkin Lymphoma

EA4HP26-LYWS-386

Atypical CD30+, EBV+ B-cells in a background of lymphohistiocytic infiltrate

Dr. Matan D. Kadosh, Dr. Vrinda Shenoy, Dr. Wen Fan

Mount Sinai Morningside/West, Pathology, New York, USA

Case Description

- 84 y.o. male with history of prostate cancer (s/p RT 10 years ago) and enlarged supraclavicular lymph node that showed EBV+ lymphohistiocytic disorder with clusters of GMS+, PAS+ budding yeast (3-5 microns).
- He presented to the emergency and was admitted for acute dyspnea on exertion that started episodically 2-6

months prior accompanied by unintentional weight loss and decrease in mobility. On admission he suffered from pancytopenia and hypercalcemia.

- The EBV Quantitative PCR of Plasma was 15900 IU/mL (high).
- Computer tomography of the neck showed a 2 cm soft tissue mass in the left supraclavicular region superior to the left subclavian vein with bilateral lymphadenopathy and lymph nodes measuring up to 1.8 cm on the left.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The specimen is composed of two small core biopsy showing predominantly histiocytes, scattered small lymphocytes, scattered neutrophils, and rare plasma cells. Scanty large, atypical cells resembling Reed-Sternberg-like cells are seen.

Immunophenotype

The atypical large cells are positive for CD30, CD20, PAX5, OCT2, MUM-1 and negative for CD3, ALK1, and BOB-1. The background histiocytes are positive for CD68, CD163, CD4 (focal), lysozyme (focal), with a small subset expressing CD1a and S100. Additional negative stains included GMS, PAS, CMV, MUCIN, HHV8, CAM5.2, CD117, CD34, MPO, CD23, and CD21/35.

Cytogenetics

Cytogenetic results are consistent with a NORMAL male 46, XY karyotype. Clonal rearrangements are NOT detected. Array results are consistent with a NORMAL male genotype. No pathogenic deletions, duplications, or extended regions of homozygosity are detected.

Molecular Studies

- TET2* p.R1359S NM_001127208.2: c.4075C>A, Missense, Pathogenic, Variant Allele Frequency (%) 31.8, Read Depth 3933.
- Positive for clonal Immunoglobulin Heavy Chain (*IGH*) gene rearrangement (V and J regions).
- Negative for clonal Immunoglobulin Light Chain (*IGK*) gene rearrangement (V and J/Kde regions).
- No discrete clonal rearrangements were detected, consistent with a polyclonal T-cell population.

Proposed Diagnosis

- Atypical CD30+, EBV+ B-cells in a background of lymphohistiocytic infiltrate in a limited biopsy specimen (see note).

Note:

Overall, the findings can be seen in a classic Hodgkin's lymphoma vs EBV associated polymorphic lymphoproliferative disorders (LPDs) arise in patients with immune deficiency or dysregulation. The diagnosis cannot be established on this limited biopsy specimen.

Interesting Feature(s)

- The patient had and EBV+ CD30+ B-cell process with abundant histiocytes and that can be seen in the setting of Classic Hodgkin lymphoma or more likely an EBV associated polymorphic lymphoproliferative disorder, PMID: 2845789.
- These B-cells were positive for clonal Immunoglobulin Heavy Chain (*IGH*) gene rearrangement (V and J regions) and the patient had an underlying *TET2* mutation.
- Given the difficulty and variety of these types of malignancies, the etiology of this disease is uncertain, PMID: 28395107.

Panel Diagnosis: classic Hodgkin lymphoma CD20+ versus EBV+ LPL, not conclusive in small biopsy

Lymphocyte Rich Classic Hodgkin Lymphoma: ask for excision biopsy.

Dr. Anurag Joshi

University Hospital of Wales, Cellular Pathology, Cardiff, UK

Case Description

43M, smoker (15 cigarettes/ day), teetotal

12 week history of right sided neck lump that has increased in size- non tender, not painful, no preceding illness

No night sweats, but feels hot all the time

No history of travel outside the UK for 7 years

History of migraines for 8 years

Ultrasound neck: 2 pathological nodes in the right neck 4cm and 3.4cm level II and level III. Thyroid and salivary gland unremarkable.

Core biopsy performed- difficult to establish a diagnosis on core as scattered Hodgkin cells seen on morphology but proliferation index in background T cells appeared high (up to 40%). T cell population showed variable TFH marker positivity (PD1, ICOS). Differential diagnosis on core: Classic Hodgkin Lymphoma, Nodular lymphocyte predominant Hodgkin lymphoma, T follicular helper cell lymphoma.

Excision biopsy was requested.

Biopsy Fixation Details

Right neck excision biopsy: multiple nodular pieces together 45x45x20mm. Fixative: neutral buffered formalin overnight.

Frozen Tissue Available

no

Details of Microscopic Findings

lymph node profiles with loss of normal architecture. vague nodularity is appreciated. Nodules are composed of small lymphoid cells. A polymorphous background is noted containing small lymphoid cells, histiocytes (with occasional the granulomas), plasma cells, scattered inter-nodular eosinophils and large blasts with prominent nucleoli including occasional binucleate and multinucleate forms resembling Hodgkin and Reed-Sternberg cells. Some blasts resemble L&H/ Popcorn cells.

Immunophenotype

CD3 stains extensive small T-cell infiltrate in the background whilst CD20 highlights abundant positivity within B-cell nodules and scattered small B cells in between the nodules. The large blasts are PAX 5 weak positive, CD45 negative, CD30 positive, CD15 focal positive, EMA negative, BCL 6 weak positive, MUM 1 positive, OCT2 negative/weak positive, CD3 negative, CD20 negative.

CD57 stains only few scattered positive cells in the background.

PD 1 highlight extensive positivity within T cells and rosettes of PD 1 positive T cells are seen around the large blasts. ICOS stains a subpopulation of the T cells with ICOS positivity in the T-cell rosettes.

CD21 highlights disrupted and expanded follicular dendritic cell mesh works supporting the B-cell nodules.

Background T cell population shows abundant CD4 staining. Ki-67 staining highlights large blasts and proliferation index within the T-cell component also appears increased (up to 40%). ISH for EBER is negative.

Cytogenetics

not performed

Molecular Studies

T cell PCR was performed on core biopsy specimen using BIOMED II primers: T-cell polyclonality detected NGS was performed (TSO500, 4 gene panel analysed) on core biopsy specimen: no variants detected in TET2, RHOA, DNMT3A or IDH2.

Proposed Diagnosis

lymphocyte rich classic Hodgkin lymphoma

Interesting Feature(s)

- Hodgkin and Reed-Sternberg-like cells (mononucleate, binucleate and multinucleate forms) and occasional blasts that resemble L&H cells (popcorn cells)
- Mixed background infiltrate with eosinophils, plasma cells, histiocytes- some small granulomas also seen.
- patient recruited to RADAR trial, Brentuximab-AAVD arm (experimental arm) and has responded with complete metabolic response (PET scan) after second cycle.
- Patient has completed third cycle with dose reduction of Brentuximab Vedotin for grade 2 peripheral neuropathy

Panel Diagnosis: Lymphocyte-Rich classic Hodgkin Lymphoma

EA4HP26-LYWS-412

Concealed Primary Bone Marrow Hodgkin Lymphoma with extensive Histiocytic Infiltration, Hemophagocytic Lymphohistiocytosis and acute fatal course

Dr. Dina Soliman¹, Dr. Sara Elkorashi², Dr. Aliaa Amer¹

¹ Hamad medical corporation, Doha, Qatar/ National Cancer institute, Cairo University, Cairo-Egypt, Department of laboratory medicine and pathology, Doha, Qatar; ² Hamad medical corporation, Doha, Qatar, Doha, Qatar

Case Description

A 46-year-old man presented with 10 days of abdominal pain, fever, and was diagnosed with chronic liver disease and primary sclerosing cholangitis after ERCP. He was febrile, emaciated, jaundiced, hypotensive, and had hepatomegaly with ascites on exam. Labs showed severe pancytopenia (WBC $1.1 \times 10^3/\mu\text{L}$, neutrophils $0.6 \times 10^3/\mu\text{L}$, platelets $23 \times 10^3/\mu\text{L}$), elevated liver enzymes, LDH of 410 U/L, and serum ferritin over 15,000 ng/ml.

A virology screen showed that the EBV PCR was positive (146,698 IU/ml). Based on both clinical presentation and laboratory findings, Hemophagocytic Lymphohistiocytosis (HLH) was suspected. Methylprednisolone treatment was initiated and a bone marrow examination was performed. The patient's condition worsened, developing acute kidney injury and disseminated intravascular coagulation (DIC). On the ninth day of admission, the patient suffered cardiac arrest and was pronounced dead. Afterwards, the bone marrow biopsy confirmed extensive Hodgkin Lymphoma (HL) with marked hemophagocytic activity.

Biopsy Fixation Details

BM biopsy: AZF-fixed

Frozen Tissue Available

N/A

Details of Microscopic Findings

The peripheral smear demonstrates severe pancytopenia. Bone marrow aspirate is notably hypocellular, showing reduced trilineage hematopoiesis. Occasional histiocytes actively engaged in erythrophagocytosis are observed. The architecture of the bone marrow biopsy is distorted revealing multiple large areas of abnormal infiltrate composed predominantly of histiocytes, with some T-lymphocytes present within fibrotic tissue. Residing within these histiocytic infiltrates, numerous large atypical cells are evident, including Reed-Sternberg cells, multinucleated giant RS cells, mononuclear Hodgkin cells, popcorn cells, and lacunar cells, both isolated and in clusters. Some hypocellular bone marrow spaces exhibit suppressed trilineage hematopoiesis alongside extensive histiocytic infiltration characterized by massive erythrophagocytosis. There is also a marked, diffuse increase in reticulin fibrosis, graded at 2-3 out of 3.

Immunophenotype

IHC: CD30 and CD15 immunostains highlighted large sheets and clusters of Hodgkin's cells; some of which show the characteristic membrane & paranuclear dot-like positivity. These large cells show partial positivity for CD20 and PAX-5 (weak) while negative for CD79 and CD45. The neoplastic cells reside within large sheets of histiocytes showing strong positivity for CD68, CD163 and S100. EBER: positive in large cells.

Cytogenetics

Not done

Molecular Studies

Not done

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte depleted associated with dense histiocytic infiltration and massive hemophagocytosis

Interesting Feature(s)

This case is both diagnostically complex and morphologically interesting. Primary bone marrow HL is rare, usually found in HIV-positive patients and linked to aggressive clinical course. Lymphoma was not clinically suspected due to absent lymphadenopathy and overlapping symptoms from EBV infection, sepsis, and cytokine storm associated with macrophage activation syndrome. Diagnosis was complicated by extensive erythrophagocytosis occupying large areas of the marrow and somehow masked the presence of lymphoma. Hodgkin lymphoma was hard to identify, given the dense histiocytic infiltration, pronounced hemophagocytosis, and lack of the typical mixed cellular infiltrate made identifying Hodgkin lymphoma challenging.

Panel Diagnosis: Primary Bone Marrow classic Hodgkin lymphoma associated with Hemophagocytic Lymphohistiocytosis

EA4HP26-LYWS-415**Extranodal Classic Hodgkin Lymphoma of Maxillary Sinus**

Dr. Pravin Mahajan, Dr. Vivek Parameshwar, Dr. Maria A. DeSouza

S L Raheja Hospital, Histopathology, Mumbai, India

Case Description

A 39-year-old male complained of chronic sinusitis. The CECT neck showed features suggestive of sinusitis with right submandibular lymph node enlargement. Right maxillary sinus biopsy was done.

The histopathology was reported as an EBV associated mucocutaneous ulcer of the maxillary sinus mucosa.

The lymph biopsy done after a month was reported as an EBV associated lymphoproliferation.

These diagnoses were made in another hospital.

The patient presented with a right maxillary swelling within ten months post lymph node biopsy. The CECT revealed a heterogeneously enhancing soft tissue mass lesion involving the right maxillary sinus with extension into the ipsilateral ethmoid sinus and nasal cavity. The lesion measured 6.7x4.7 cm. Multiple non-necrotic right cervical lymph nodes were seen at the levels Ib, IIA, IIb and III with the largest measuring 1.9x1.8 cm in the right level IIb.

The patient underwent endoscopic resection of the mass.

We received multiple firm, grey white tissue bits, some of which appeared polypoidal, aggregating to 8x6x3.2 cm.

Biopsy Fixation Details

The specimen was fixed in 10% neutral buffered formalin for 24 hours.

Frozen Tissue Available

Not available

Details of Microscopic Findings

The histological examination showed polypoidal bits lined by sinonasal mucosa with mucosa being largely ulcerated. The submucosal tissue revealed a vaguely nodular and diffuse lymphoproliferation destroying the bone and also invading the adjacent skeletal muscles and subcutaneous adipose tissue.

The infiltrate composed of numerous mononucleated Hodgkin and binucleated and multilobate RS-like cells amidst a polymorphous population of lymphocytes, plasma cells and eosinophils. Foci of necrosis were seen.

Immunophenotype

The Hodgkin and RS-like cells expressed CD30, CD15, PAX5, STAT6 immunostains and EBERs by ISH. They were immunonegative for CD20, CD3, OCT2, BOB1, CD79a, ALK1 and LCA.

Cytogenetics

Not done

Molecular Studies

Not done

Proposed Diagnosis

Extranodal classic Hodgkin lymphoma of mixed cellularity type

Interesting Feature(s)

The maxillary sinus is a very rare site for extranodal classic Hodgkin lymphoma (CHL).

In view of only mucosal involvement with no tissue destruction seen at the time of initial presentation, the case was diagnosed as an EBV associated mucocutaneous ulcer on limited biopsy material available for histology. The lymph node enlargement was also considered to be a part of spectrum of EBV associated lymphoproliferation not amounting to lymphoma.

However, obvious tissue destruction seen in histology of endoscopic resection in conjunction with immunoprofile of RS-like cells, it was relatively easy to make a diagnosis of CHL on excision material.

Overall, it is very difficult to make a diagnosis of CHL at the extranodal sites in the absence of tissue destruction and on small biopsies, especially when associated with EBV.

Panel Diagnosis: No pictures- no classification/diagnosis possible

EA4HP26-LYWS-418

An unusual case of classic Hodgkin lymphoma with partial CD30 expression

Priv.-Doz. Elena Gerhard-Hartmann, Prof. Ioannis Anagnostopoulos, Prof. Alberto Zamò, Dr. Stefan Kircher, Priv.-Doz. Stephanie Brändlein, Priv.-Doz. Katja Maurus, Prof. Andreas Rosenwald

University of Wuerzburg, Institute of Pathology, Wuerzburg, Germany

Case Description

A 30 year old man presented with cervical and axillary lymphadenopathy. An initial small biopsy from a cervical lymph node revealed a PAX5+/CD30- lymphoma morphologically suspicious of classic Hodgkin lymphoma (cHL). Due to quantitative limitations of the biopsy material, a definitive diagnosis could not be established. Consequently, an enlarged axillary lymph node was excised and submitted for consultation (present material). There was no known history of lymphoma.

Biopsy Fixation Details

4% buffered Formaldehyde

Frozen Tissue Available

no

Details of Microscopic Findings

The lymph node architecture was effaced by a partially necrotic infiltrate composed of small lymphocytes, abundant histiocytes, and granulocytes. In addition, numerous, often quite densely packed large cells were present, many of which were partially bi- or multinucleated and morphologically reminiscent of Hodgkin/Reed–Sternberg (HRS) cells.

Immunophenotype

The HRS-like cell population showed only partial, weak to moderate CD30 and a frequent CD15 expression. The B-cell immunophenotype was incomplete with weak to moderate, yet consistent expression of PAX5, while expression of CD20, CD19, CD79a/b, OCT2, and CD45 was absent. There was no expression of EBV-encoded LMP1, CD3, perforin, or ALK/CD246.

Cytogenetics

not done

Molecular Studies

Ig/TCR clonality analyses (EuroClonality protocol) showed a clonally expanded B-cell-population (monoallelic rearrangement with polyclonal background for IGH VH–JH Tube B), but also a clonally expanded T-cell-population (TCRB: Tube A reproducible product, Tube C monoallelic rearrangement with polyclonal background). A custom panel-based next generation sequencing analysis (using the protocol described in PMID: 37664054) revealed 4 pathogenic/likely pathogenic mutations: one each in *TNFAIP3* (exon 7) and *NFKBIE* (exon 1) (allelic fraction 6%) and two (in cis) in exon 2 of the *SOCS1* gene (allelic fraction 7%).

Proposed Diagnosis

Classic Hodgkin lymphoma (cHL, EBV-negative), mixed cellularity with unusual partial expression of CD30.

Interesting Feature(s)

This case represents a lymphoma that, based on the integrated morphologic, immunophenotypic, and molecular findings, is in our view best classified as cHL with an unusual immunophenotype characterized by only partial CD30 expression in the absence of prior therapy. CD30 expression is generally regarded as a diagnostic cornerstone of cHL, and its absence in cases otherwise compatible with cHL may result in significant diagnostic challenges, as illustrated by the initial limited biopsy in this patient. Nevertheless, heterogeneous CD30 expression in cHL has been reported, and rare cases with absent CD30 expression have also been described (e.g., PMID: 9777980; PMID: 40907344). Notably, mutational analysis of this tumor cell-rich specimen revealed a genetic profile supportive of cHL, underscoring the diagnostic utility of contemporary molecular approaches in resolving challenging cases.

Panel Diagnosis: classic Hodgkin lymphoma (EBV-negative), with unusual immunophenotype (partial expression of CD30), mixed cellularity

EA4HP26-LYWS-422

A Challenging Case of a High-Grade CD30-positive Lymphoma

Dr. Bhanupriya Kakarala, Dr. Fatima M.A. Khan, Dr. Amer Wahed, Dr. Andy Nguyen, Dr. Hanadi E. Achi, Dr. Brenda Mai

McGovern Medical School at The University of Texas Health Science Center at Houston, Pathology and Laboratory Medicine, Houston, USA

Case Description

33-year-old female with a mediastinal mass and left supraclavicular mass.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

Not available

Details of Microscopic Findings

- Histological sections show diffuse sheets of large atypical cells with multinucleation or horseshoe-shaped nuclei and prominent cherry red nucleoli.
- Areas with extensive necrosis are seen.

Immunophenotype

POSITIVE	NEGATIVE
CD30 (strong and diffuse)	CD23
MUM1	ALK1
CD15 (small subset weak)	CD138
	CD45
	GATA3
	P63
	EMA
	All T-cell markers (CD2, CD3, CD4, CD5, CD7, CD8, CD43, CD56, TIA, perforin, granzyme B)
	All B-cell markers (CD20, CD79a, BOB1, OCT2, PAX5)

Cytogenetics

The patient had a normal female karyotype on the bone marrow staging specimen 46,XX.

Molecular Studies

- ALCL FISH was inconclusive.

Proposed Diagnosis

- High grade CD30-positive lymphoma
- The differential diagnosis included:
 1. ALK-negative anaplastic large cell lymphoma null type
 2. Classic Hodgkin lymphoma
 3. PMBCL-like grey zone lymphoma
- This case was sent to MD Anderson Cancer Center (MDACC) for consultation and the biopsy was deemed to be consistent with classic Hodgkin lymphoma.

Interesting Feature(s)

- CHL (Classical Hodgkin Lymphoma) and ALCL (Anaplastic Large Cell Lymphoma) are both CD30-positive lymphomas that can look similar under the microscope with large atypical multinucleated cells, making differentiation difficult; CHL is a B-cell lymphoma (though often losing B-cell markers except a dim PAX5), while ALCL is a T-cell lymphoma.
- ALK-negative ALCL often presents as a more aggressive lymphoma and can mimic CHL, requiring careful diagnosis via immunohistochemistry (IHC) and FISH testing (e.g., ALK, DUSP22, TP63).
- This case was a diagnostic challenge as it did not express B-cells or T-cell markers; in addition, CD30 expression was strong and diffuse in this case, unlike the normal heterogeneous staining that is typically seen in classic Hodgkin lymphoma (CHL).
- The case also had necrosis which suggested a higher grade lesion and favored ALCL.
- This case represents a difficult case of CHL with loss of all B-cell markers, strong diffuse expression of CD30, and focal areas of necrosis, creating a diagnostic challenge.

Panel Diagnosis: Classic Hodgkin Lymphoma with unusual phenotype (PAX5-)

Does extra-mediastinal Grey Zone Lymphoma exist ?

Dr. Catherine Chassagne-Clement¹, Dr. Julie Gervasoni², Dr. Emmanuel Beillard³, Dr. Yann Guillermin⁴

¹ Centre Léon Bérard, Biopathologie, Lyon, France; ² Centre Léon Bérard, Biopathologie, Lyon, France; ³ Centre Léon Bérard, Biopathologie, Lyon, France; ⁴ Centre Léon Bérard, Oncohématologie, Lyon, France

Case Description

A 67-year-old female presented in 11/2022 with B symptoms, bone lesions and biological abnormalities (elevated LDH, anemia, hepatic cytolysis). The FDG PET imaging revealed a hypermetabolic disease (SUV max 25) in supra- and infra-diaphragmatic lymph nodes, spleen, liver and bones. The lymph node surgical biopsy (inguinal) resulted in the diagnosis of a CD20- Grey Zone Lymphoma (GZL) with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma. After 6 cycles of CHOP therapy, she went into complete remission but relapsed 4 months later in 07/2023 with the same histology on a iliac surgical lymph node biopsy. She died 4 months later after salvage chemotherapy.

Biopsy Fixation Details

4% neutral buffered formol

Frozen Tissue Available

Yes

Details of Microscopic Findings

Microscopic findings were similar between the 2 samples (2022 and 2023).

The normal lymph node architecture was diffusely effaced without fibrosis and capsular thickening. Large lymphoma cells with Reed Sternberg and Hodgkin morphology were dispersed in a polymorphic background. This inflammatory infiltrate included a large component of epithelioid histiocytes and small lymphocytes.

Immunophenotype

The large lymphoma cells were stained with PAX5, OCT2, MUM1, BCL6 antibodies but were negative for CD20, CD19, CD79a, CD30, BCL2, CD10 and GATA3. There was a weak and focused staining for CD15, EMA, CD2 and CD4 markers. The Ki67 proliferative index was high (80%). There was no association with EBV by *in-situ* hybridization.

Cytogenetics

FISH analysis with break-apart probes for BCL2, BCL6, MYC and CD274 genes were performed. An isolated BCL2 rearrangement was identified without rearrangement for BCL6, MYC, CD274. However, there was a gain of 9p24 (5 copies).

Molecular Studies

A PCR analysis (BIOMED-2 protocol) identified a clonal immunoglobuline gene rearrangement for FR2 and Vk-Jk but no TCR gene rearrangement was found.

A NGS study using a Hematology custom panel of 150 genes revealed several pathogenic/likely pathogenic variants : ARID1A (NM_006015.6) Exon 20: c.5548dup, p.(D1850Gfs*4) [vaf.: 3.2%, 1250x], CREBBP (NM_004380.3) Exon 26: c.4336C>T, p.(R1446C) [vaf.: 5.8%, 1807x], KMT2D (NM_003482.4) Exon 9: c.1017G>A, p.(W339*) [vaf.: 6%, 1615x], KMT2D (NM_003482.4) Exon 40: c.12257_12261del, p.(P4086Lfs*19) [vaf.: 3.9%, 1402x], TNFRSF14 (NM_003820.4) Exon 2: c.174del, p.(P59Qfs*5) [vaf.: 3%, 564x], TP53 (NM_000546.6) Intron 9 c.993+2T>A, p.(?) [vaf.: 3.9%, 1097x].

Proposed Diagnosis

CD20 negative Diffuse Large B-cell Lymphoma mimicking an extra-mediastinal Grey Zone Lymphoma.

Interesting Feature(s)

The 5th WHO classification recognizes the GZL as a lymphoid tumor with overlapping features between DLBCL and CHL, with a close relationship to PMBL based on histological markers. However, depending on the clinical presentation, GZL may correspond to different entities with specific genomic profiles and pathogenic mechanisms. Here we describe a case of extra-mediastinal GZL with hybrid features between DLBCL and CHL and a large component of histiocytes but the molecular profile would fit best with that of a DLBCL. This case could illustrate the underlying biology between these different entities.

Panel Diagnosis: Not classified (classic Hodgkin lymphoma like features, BCL2 R, Mutational pattern of B cell lymphoma) Few pictures to classify

EA4HP26-LYWS-433

Cytotoxic marker-positive classic Hodgkin Lymphoma, EBV negative, in an autoimmune/therapy-related setting.

Dr. Eric Davenne, PhD/MD Luis Veloza Cabrera, PhD/MD Bettina Bisig, Prof. Laurence de Leval

Centre hospitalier universitaire vaudois, Institute of Pathology, 1011, Switzerland

Case Description

An asymptomatic 61-year-old male, with an autoimmune cirrhosis treated by azathioprine (150 mg/day) for 8 years, was found with multiple abdominal lymphadenopathies, discovered on a follow-up MRI, with high SUV (from 13.9 to 30.4) on PET-CT. Normal blood count and increased LDH 244 UI/L. A needle core biopsy revealed an atypical lymphoid proliferation rich in T cells, showing partial loss of CD7 and BCL2, with a few larger cells diffusely positive for CD30 and partially for CD15, suspicious for either a T-cell lymphoma or a classic Hodgkin lymphoma. TR and IG clonality analysis (PCR-based) were negative. No mutation detected by NGS (142 genes panel). Surgical excision of an iliac lymph node was performed.

Biopsy Fixation Details

Needle core biopsies: one biopsy in B-Plus Fix™, two biopsies in buffered formalin (10%)

Lymph node excision: one slice in B-Plus Fix™, the rest in buffered formalin (10%), total inclusion.

Only the lymph node excision is submitted to the workshop.

Frozen Tissue Available

Samples from the lymph node excision.

Details of Microscopic Findings

A large lymph node limited by a thin fibrous capsule. The architecture is obscured by a polymorphic cell population with a diffuse and vaguely nodular architecture, comprising a background of small lymphocytes mixed with mature plasma cells, immunoblasts, and numerous histiocytes often grouped in small clusters. Within this polymorphic cellular background are a few atypical medium to large sized cells with moderately abundant cytoplasm, oval nuclei, nucleoli, sometimes bilobed or multilobed, and vesicular chromatin. Some of these cells have a Hodgkin or Reed-Sternberg morphology. Other cells show a degenerative appearance with condensed cytoplasm and chromatin ("mummified cells"). The large atypical cells are scattered, without syncytial areas. There is no necrosis and no eosinophilia. The lymphoproliferation is focally dissociated by bands of interstitial sclerosis, but there is no nodular dissection by fibrous trabeculae.

Immunophenotype

Hodgkin and Reed-Sternberg cells (HRS) are positive for CD30, MUM1 and Perforin, partially positive for CD15, but negative for T-cell markers (CD2, CD3, CD4, CD5, CD7 and CD8) and other cytotoxic markers (TIA1, granzyme).

HRS cells show variable positivity for B-cell markers (OCT2, CD20, PAX5, BOB1). The background is rich in small T cells (mainly CD4+), histiocytes and plasma cells. In situ hybridization for EBV (EBER) is negative.

Cytogenetics

Not performed

Molecular Studies

Only performed on core biopsy : clonality assays (PCR): no clonal IG or TR rearrangement detected ; NGS (142 genes panel) : no mutation detected.

Proposed Diagnosis

- Classic Hodgkin Lymphoma, EBV negative, autoimmune/therapy-related setting (WHO5)
- Other iatrogenic immunodeficiency-associated lymphoproliferative disorder of classic Hodgkin Lymphoma type, EBV negative (ICC 2022)

There is isolated expression of cytotoxic marker in HRS cells. Histological subtype is consistent with lymphocyte-rich. Patient with Ann Arbor stage IIIa, treated with brentuximab, vedotin, doxorubicin, vinblastine, and dacarbazine, with near complete response at 12 months follow-up.

Interesting Feature(s)

Expression of cytotoxic markers in classic Hodgkin Lymphoma (cHL) is very rare and is associated with a more aggressive clinical behavior and a reduced overall survival. In small sized biopsies cHL with expression of T-cell or cytotoxic markers challenges the distinction from T-cell lymphoma. Another unusual feature is EBV negativity since most cases of other iatrogenic immunodeficiency-associated lymphoproliferative disorders of cHL type are EBV positive.

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV negative) with expression of cytotoxic molecule, autoimmune /therapy-related setting

EA4HP26-LYWS-434

Challenging diagnosis of a classic Hodgkin lymphoma, lymphocyte rich subtype

Dr. Raidelys Avila Diaz, Dr. Wei Xei

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Case Description

68-year-old male with a history of stage IV nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), diagnosed via excisional biopsy after presenting with neck pain. A follow up PET/CT demonstrated an enlarged and hypermetabolic right supraclavicular LNs, highly suspicious for active lymphomatous disease. A US-guided biopsy of the supraclavicular lymph node demonstrated an atypical lymphoid infiltrate with increase in CD20 positive B-cells, suspicious for involvement of a low-grade B-cell lymphoma but not diagnostic. A subsequent excisional biopsy was diagnostic for lymphocyte rich classic Hodgkin lymphoma, consistent with stage IV lymphocyte risk classic Hodgkin's lymphoma.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

none

Details of Microscopic Findings

Sections of the lymph node show an altered nodal architecture by an atypical lymphoid infiltrate with a largely diffuse pattern. The infiltrate is composed of small lymphocytes, histiocytes and scattered large, atypical cells, some of which

show prominent nucleoli, vesicular chromatin and binucleation, resembling Hodgkin/Reed-Stenberg cells. Focal areas of dense fibrosis are noted

Immunophenotype

The large Hodgkin/Reed-Stenberg cells are positive for dim PAX5, CD30 and CD43; while negative for CD15, CD79a, CD163, bcl6. The atypical cells are present in a B-cell rich background but are surrounded by clusters of T-cells. PD1 stains numerous background T cells, some forming T cells rosettes. Kappa and lambda stain polytypic plasma cells. EBER is negative. CD20, PAX5 stains the B-cells in follicular and interfollicular patterns. CD3, CD5, CD43, CD45 and bcl-2 highlight interfollicular T-cells. CD10 and bcl6 highlight scattered TFH cells. CD138 and MUM1 highlight scattered plasma cells, which are polytypic by KAPPA/LAMBDA ISH.

Cytogenetics

None

Molecular Studies

B cell IGH and IGK gene rearrangement were performed on the FFPE, there is no convincing evidence of any clonal antigen receptor gene rearrangements using Ig heavy chain and Ig kappa chain PCR primers. The data does not support the presence of a B-cell clone in this sample. T cell TCR gamma and TCR beta gene rearrangement were performed on the FFPE, there is a predominantly polyclonal amplicon distribution at most T cell receptor gamma and beta loci. The data does not support the presence of a TB-cell clone in this sample.

Proposed Diagnosis

Classic Hodgkin lymphoma, lymphocyte rich subtype

Interesting Feature(s)

This case illustrates a rare and challenging diagnosis in a patient with a previous diagnosis of nodular lymphocyte predominant Hodgkin lymphoma. NLPHL has a different history and response to therapy than CHL, especially in stages I-II. The lesional cells have occasional morphology overlapping features of LP cells making NLPHL a reasonable differential. The immune microenvironment is composed of B cells, T cells with frequent rosettes around the neoplastic cells and histiocytes, finding suggestive of other entities such as THRLBCL and nTFHL- AI.

Panel Diagnosis: Difficult case between classic Hodgkin lymphoma lymphocyte-rich and nodular lymphocyte-predominant ; Panel can not do a formal diagnosis with the material

EA4HP26-LYWS-440

A difficult case of an EBV-positive lymphoproliferative disorder in the lung

Swati Gite, Fatima Khan, Amer Wahed, Andy Nguyen, Jacob Armstrong, Brenda Mai

University of Texas Health Science Center, Pathology and Laboratory Medicine, Houston, USA

Case Description

- 73-year-old female with a left lower lobe lung mass and mediastinal adenopathy.
- The patient had not received immunosuppressive therapy or a transplant.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

None

Details of Microscopic Findings

Lymph node:

- Microscopy revealed partial to complete effacement of lymph node architecture by a polymorphous lymphoid infiltrate composed of histiocytes, small lymphocytes, plasma cells, immunoblasts, and scattered large atypical B

cells.

- The large cells showed vesicular nuclei with prominent cherry red nucleoli and occasional Reed–Sternberg–like morphology, set within a reactive T-cell–rich background.
- EBV infection was confirmed by EBER in situ hybridization in the large atypical cells.

Lung:

- Histological sections show lung parenchyma with diffuse infiltration by a polymorphous infiltrate with histiocytes and B and T lymphocytes with focal scattered clusters of large atypical cells that have prominent cherry red nucleoli.
- There is focal angiodestruction.

Immunophenotype

Lymph node:

- The atypical large cells showed variable PAX5 expression (dim to positive) but were negative for all other B-cell markers and were positive for CD30 and MUM1.
- EBER in situ hybridization was positive in the large atypical cells and scattered small lymphocytes; ALK and cyclin D1 were negative.
- Ki-67 was increased in the large cells.

Lung:

- The atypical large cells showed variable PAX5 expression (dim to positive) and were positive for CD30 and MUM1, while CD10 and BCL6 were negative, with no germinal centers identified.
- EBER in situ hybridization was positive in the large atypical cells and scattered small lymphocytes.
- Ki-67 was increased in the large cells.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

- EBV-positive lymphoproliferative disorder
- The differential diagnosis included:
- Age-related EBV-positive lymphoproliferative disorder
- Lymphomatoid granulomatosis
- Classic Hodgkin lymphoma
- This case was sent to the NIH for consultation where it was signed out as an EBV-positive lymphoproliferative disorder.

Interesting Feature(s)

- Classic Hodgkin Lymphoma (CHL) and Epstein-Barr Virus Lymphoproliferative Disorder (EBV LPD) are distinct clinical entities with different prognoses and clinical management strategies, despite some overlapping features, especially in older or immunocompromised patients. Distinguishing EBV+ polymorphic LPD, is often difficult to separate from EBV+ CHL due to morphological similarities.
- EBV+ LPDs often occur in the context of immunodeficiency, such as age-related immunosenescence or iatrogenic immunosuppression (such as after organ transplant or methotrexate use). While EBV+ CHL can also occur in these settings, it is defined by specific histological and immunophenotypic criteria.
- This case was challenging diagnostically; the immunophenotype on the core biopsy and the lung wedge had different expressions of the B-cell IHC markers. In addition, there were focal areas that had angioneclerosis that was concerning for lymphomatoid granulomatosis.
- The case was assumed to be an age-related EBV+ LPD clinically as the patient's symptoms resolved after excision of the lung wedge and the PET/Ct imaging did not show other hotspots. The patient will undergo close clinical follow-up.

Panel Diagnosis: Classic Hodgkin lymphoma (EBV-positive) Arguments against EBV+ LPD is incomplete B-cell immunophenotype

An Unusual Recurrent/Relapsing Case of EBV+ Classic Hodgkin Lymphoma

Dr. Moinul Haque¹, Dr. Aron Flagg², Dr. Deepika Kumar¹

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Case Description

- 24-year-old male presented with enlarged right cervical lymph node; biopsy showing EBV+ Classic Hodgkin Lymphoma (CHL).
- PMH: 2 prior episodes of CHL previously s/p autologous stem cell transplant (ASCT) and Brentuximab maintenance.
- 12 years back, he presented with 2-week history of fevers, fatigue and weight loss. PET scan revealed extensive lymphadenopathy and multi-organ involvement. Cervical lymph node biopsy revealed CHL, EBV+. He was treated with ABVE-PC (Doxorubicin, Bleomycin, Vincristine, Etoposide, Prednisone, and Cyclophosphamide) x 4 cycles followed by radiation.
- First relapse: 4 years later, he presented with 20 lb weight loss, fevers, and abdominal pain. Imaging showed large abdominal mass, widespread lymphadenopathy, and multi-organ involvement. Biopsy revealed CHL, favoring Nodular Sclerosis subtype, EBV+. Bone marrow involvement noted. He received chemotherapy, followed by ASCT, and Brentuximab maintenance for 3 months.
- 2 years later, immunodeficiency workup showed low CD4 count, low immunoglobulin levels (IgG and IgA), and elevated CD19+B-cells. He was started on IVIg. DNA sequencing detected pathogenic variant for *MAGT1*, associated with XMEN disease (X-linked immunodeficiency with magnesium defect, Epstein–Barr virus [EBV] infection and neoplasia).
- Current Clinical Course: Started on brentuximab/bendamustine followed by allogeneic 10/10 MSD BMT, with complex recovery course.

Biopsy Fixation Details

Lymph Node Biopsy: 10% formalin fixation

Frozen Tissue Available

-

Details of Microscopic Findings

Effacement of lymph node architecture by an atypical polymorphous infiltrate, forming an occasional nodule surrounded by sclerotic bands. Infiltrate composed of small lymphocytes, eosinophils, numerous histiocytes, occasional plasma cells and interspersed Hodgkin/Reed-Sternberg cells and their variants.

Immunophenotype

Markers Expression

CD30	Positive
CD15	Positive
PAX5	Weak
Fascin	Positive
EBER-ISH	Positive
CD45	Negative

CD3 Negative

CD20 Negative

Cytogenetics

-

Molecular Studies

- A likely pathogenic variant found in *MAGT1*, :c.859-2A>G (hg19: X:77109463). Immunodeficiency, X-linked, with magnesium defect, Epstein-Barr virus infection and neoplasia (XMEN)

Proposed Diagnosis

- Classic Hodgkin Lymphoma, EBV+, Inborn error of immunity-associated

Interesting Feature(s)

- This pediatric patient had multiple relapses of EBV+ Classical Hodgkin Lymphoma despite frontline ABVE-PC, which typically has curative effect. This trajectory with chemoresistance and immune escape is highly unusual for typical pediatric CHL.
- Immunologic workup revealed CD4 lymphopenia, elevated CD19, and IgG/IgA deficiency. Genetic workup identified an inborn error of immunity, XMEN disease (likely pathogenic variant *MAGT1* c.859-2A>G). XMEN disease is a primary X-linked immunodeficiency characterized by impaired Mg²⁺ transport, defective T-cell receptor signaling, and reduced NKG2D expression on NK and CD8+ T cells, which increases the tendency for recurrent EBV infections and associated neoplasms.
- Immunodeficiency flow cytometry found increased absolute NK and CD8+ T cell count during routine workup, which may be a compensatory mechanism and diagnostic clue for underlying XMEN disease. EBV infectivity was detected in all relapses over a 11-year period indicating defective clearance of EBV in this patient's by host cell-mediated immune pathways.
- Thus, this is an exceptionally rare case of inborn error of immunity (rare variant of *MAGT1*) associated CHL with the role of EBV as a persistent oncogenic stimulus. Early genetic testing to identify underlying primary immunodeficiency is crucial for appropriate management.

Panel Diagnosis: Classic Hodgkin Lymphoma(EBV+), nodular sclerosis, relapsing, inborn error of immunity associated

EA4HP26-LYWS-444

A case of lymphocyte rich classic Hodgkin lymphoma in a patient with an underlying/concomitant autoimmune disorder.

Dr. Arpan Samaddar

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Case Description

The patient is a 71/F who presented with a tender mass over her left lateral neck. She had no history of fever/night sweats/weight loss. She had a history of dermatomyositis (with a classic heliotrope rash on eyelids, chest, upper back with proximal muscle weakness and positive anti Mi-2 serology) diagnosed 11 months earlier as well as multifocal choroiditis causing legal blindness 20 years ago.

On examination, she was found to have three discrete cervical lymph nodes (Level V). PET imaging revealed extensive left cervical adenopathy involving increased FDG uptake involving levels II, III, IV and V along with scattered focal increased osseous uptake

Biopsy Fixation Details

Biopsy in FFPE blocks, 10% neutral buffered formalin

Frozen Tissue Available

None

Details of Microscopic Findings

H/E sections show a lymph node with almost effaced architecture. There is a nodular lymphocytic infiltrate consisting of mostly small mature lymphocytes with regressed germinal centers in the background. Reed-Sternberg cells are seen within the follicles but outside the germinal center. They include both classic RS cells with bilobed nucleus, vesicular chromatin and eosinophilic nucleoli, as well as “popcorn like” cells with a folded nucleus

Immunophenotype

Flow cytometry was negative for a monotypic B cell population as well as a T cell population with antigen aberrancy. Immunohistochemistry showed the RS cells to be positive for CD30, PAX-5 (dim), BCL-6, and MUM1; negative for CD15, CD20, CD79a, CD45 and Bcl-2. PD1 shows T-cells surrounding RS cells. CD20 and CD79 highlight the nodular B-cell clusters, and CD21 shows preserved dendritic network. Most of the lymph node tissue is made up of CD3/CD5/CD43+ T-cells which are mix of CD4+ and CD8+. Small background B-cells do not show abnormal staining with CD10, Cyclin D1, or BCL-2. There are background polyclonal plasma cells on CD138 IHC and kappa/lambda ISH. EBER ISH is negative.

Cytogenetics

Not applicable

Molecular Studies

T-cell and B-cell clonality studies were performed. No monoclonal B cell gene rearrangements were detected using Ig heavy chain and Ig kappa chain genes PCR primers. No monoclonal T cell gene rearrangements were detected using T cell receptor gamma and T cell receptor beta genes PCR primers.

Proposed Diagnosis

Lymphocyte rich Classic Hodgkin lymphoma

Interesting Feature(s)

This case illustrates an example of LRCHL, which is EBV negative in a patient with an underlying/concomitant systemic autoimmune disorder. There is a nodular lymphocytic infiltrate (composed of mainly T cells), with scattered RS cells. The tumor microenvironment lacks other inflammatory cells like plasma cells, eosinophils, and histiocytes. It is important to distinguish it from NLPHL as the RS cells in LRCHL may resemble LP/“popcorn” cells. The clinical course and management of these two entities are quite different. Other differentials to exclude would be SLL/CLL which may have scattered RS like cells mimicking LRCHL. Dermatomyositis has been shown to have a strong association with underlying malignancy but the association with Hodgkin lymphoma is uncommon with few cases reported in literature

Panel Diagnosis: Lymphocyte-rich classic Hodgkin Lymphoma

EA4HP26-LYWS-447

Classic Hodgkin Lymphoma, EBV-Positive, arising in Immune Deficiency/Dysregulation

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Case Description

Clinical History: A 45-year-old man with HIV infection since 2003 was diagnosed with stage IVB classical Hodgkin lymphoma (CHL), EBV-positive, with bone marrow involvement in November 2014. He initially presented with fevers, weight loss, and anemia; bone marrow biopsy demonstrated fibrotic marrow with atypical mononuclear cells, and

right axillary lymph node excision confirmed HIV-associated CHL. PET imaging in February 2015 showed hypermetabolic lymphadenopathy above and below the diaphragm and marrow involvement. His course was complicated by hemophagocytic lymphohistiocytosis with multiorgan dysfunction. He received one cycle of GemOx followed by six cycles of ABVD, completed in October 2015, achieving complete remission confirmed by PET and surveillance imaging through February 2020.

The patient remained disease-free until late 2024, when imaging revealed recurrent lymphadenopathy. PET scan on 2/25/2025 demonstrated FDG-avid lymph nodes involving the axillary, mediastinal/hilar, and retroperitoneal regions, with splenic uptake. A left axillary lymph node excisional biopsy in March 2025 confirmed recurrent classical Hodgkin lymphoma, EBV positive.

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

No

Details of Microscopic Findings

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Immunophenotype

Immunohistochemistry: Immunohistochemical studies showed that neoplastic large atypical cells are positive for CD30, CD15, dim PAX5, BCL6 and dim variable CD20. OCT2 shows dim staining in a subset of the atypical lymphoid cells. They are negative for CD45, BCL2, CD8 and CD3. BCL2 and CD4 are mostly positive in T cells. CD57 is positive in activated lymphoid T cells.

ISH for EBV encoded RNA (EBER) is positive in neoplastic cells.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Classic Hodgkin Lymphoma, Lymphocyte rich, EBV-positive, arising in Immune Deficiency/Dysregulation (HIV-infection)

Interesting Feature(s)

NLPH-like architecture and morphologic features

Panel Diagnosis: Classic Hodgkin Lymphoma, EBV+ relapse , arising in immune deficiency (HIV infection)

EA4HP26-LYWS-448

Unusual EBV-positive lymphoproliferative disorder abundant epithelioid histiocytes and overlapping features of nTFH-AI and CHL

Dr. Theresa Spivey

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Case Description

85-year-old female with history hemophilia A, DM2, HLD, HTN, neuropathy, osteoporosis, TIA, and thyroid nodules, who had longstanding lymphadenopathy (LAD) above the diaphragm for ~14 years. She presented with weakness and found new LAD of retroperitoneal and gastrohepatic lymph nodes, with widespread diffuse FDG-avid disease with evidence of extranodal involvement, including spleen and sacrum. Excisional biopsy of the parotid tail mass/cervical lymph node was performed. Notably, the enlarged parotid lesion had been previously identified at an outside institution, where a core biopsy and fine-needle aspiration previously were negative.

Biopsy Fixation Details

Submitted fresh, portion was submitted for flow cytometry analysis, remainder fixed in 10% neutral buffered formalin, processed and embedded into paraffin blocks.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Effacement of lymphoid tissue by polymorphous proliferation expanding the interfollicular space with atretic follicles. Abundant epithelioid histiocytes were present with small lymphocytes and plasma cells. Few areas show mild vascular proliferation but without arborization or sclerosis. These areas harbored atypical immunoblast-like cells, some with HRS-like morphology including multinucleated forms. Many were medium in size with rare large cells seen. Endothelial cells were very rarely identified. No epithelium or salivary parenchyma present, favoring an intraparotid or periparotid lymph node.

Immunophenotype CD30 highlights cells of variable size, mostly medium. A subset of the cells show partial weak, cytoplasmic CD20 and CD79a positivity, and weak PAX5 and OCT2 (partial). Positive MUM1, CD15, BCL6 (subset, weak), and EBER (EBV ISH), and are negative for CD45 and BOB1. PD-L1 expressed in the majority of the atypical cells (at least 70%), hard to quantitate due to background histiocytes.

The interfollicular T cells are positive for CD3 and CD4 with retained expression of CD2, CD5, and CD7. The cells are positive for ICOS and CXCL13, with preferential distribution surrounding some vessels. They are negative for CD10 and PD1. CD8-positive T cells in the background (CD4:CD8 ~2). TRBC1 without restriction. CD21 and CD35 show expansion of FDC meshworks into the interfollicular region. Kappa and lambda RNA in-situ hybridization demonstrating polytypic plasma cells. CD68 and S100 highlight background histiocytes. The Ki-67 proliferation index is increased in the interfollicular areas (50-60%).

Flow cytometry was negative for an abnormal B- or T-cell population. 16% CD19+ B cells, 81% CD3+ T cells; CD4:CD8 = 2.7; Polytypic TRBC1; No significant CD279 (PD-1) population

Cytogenetics

N/A

Molecular Studies

Negative T-cell clonality by PCR for *TCRG* and *TCRB* genes.

Targeted Lymphoid NGS panel (128-genes) performed at a reference laboratory detected a pathogenic mutation in DNMT3A p.W893* (VAF 26.0%)

Proposed Diagnosis

EBV+ Classic Hodgkin Lymphoma

Interesting Feature(s)

1. Longstanding history of LAD (>10 years), and parotid and anterior mediastinal mass for at least 2 years before symptoms
2. Background rich in epithelioid histiocytes and CD4+ cells with TFH-phenotype (ICOS+ CXCL13+), abnormal expansion and distribution of follicular dendritic cell meshworks
3. Slightly smaller size of the HRS cells, obscured by epithelioid histiocytes, but otherwise typical phenotypic profile for CHL, including downregulation of B-cell programme
4. Challenging differential including nodal TFH lymphoma (nTFH-AI) with associated B-cell hyperplasia/LPD or EBV+ associated hyperplasia/LPD

Panel Diagnosis: Classic Hodgkin Lymphoma (EBV positive) with TFH enriched background

Mediastinal Gray Zone Lymphoma with Genetic Double Hit (IGH::BCL2 + MYC)

Dr. Govind Bhagat

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Case Description

A 71 year old female with h/o HTN, GERD, osteoporosis, colon polyps, and reported thyroid cancer s/p partial thyroidectomy 10 years previously, presented with chest pain, difficulty in breathing, and weakness. Chest CT scan showed a 5 cm right hilar mass, multiple pulmonary nodules, and enlarged axillary lymph nodes (LNs). PET/CT showed widespread sites of hypermetabolic lymphadenopathy (LAD) above and below the diaphragm, SUV of the hilar mass being 39.8. Bronchoscopy revealed near total occlusion of the bronchus and collapse of the right upper lobe. The LDH level was 543 u/L and her IPI score was 4. She was deemed to have Lugano stage IV disease. Left axillary LN biopsy revealed classic Hodgkin lymphoma (CHL) and large B-cell lymphoma with a phenotypic profile indicative of mediastinal gray zone lymphoma. There has been significant reduction in LAD after 4 cycles of DA EPOCH-R therapy.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the LN showed a thickened capsule and multifocal, polymorphous cellular infiltrates composed of histiocytes, eosinophils, small mature lymphocytes, and plasma cells, with variable numbers of large atypical lymphocytes displaying Hodgkin and Reed-Sternberg (H-RS) morphology admixed. Variant H-RS cells and mummified cells were observed. Paucicellular bands of fibrosis encircled the cellular infiltrates, imparting a nodular appearance. In a few foci, numerous large centroblast-like cells were present forming large dense aggregates/infiltrates.

Immunophenotype

IHC staining showed differences in the immunophenotype of the neoplastic lymphocytes in different areas. All atypical lymphoid cells expressed CD30, CD15, PAX5(variable), and MUM1, while the staining frequency and intensity of other markers varied. In foci of large cell infiltrates, the lesion cells exhibited the following phenotype: CD45(weak), CD20(strong), OCT2(strong), CD79a(strong), CD19, BOB.1, and CD23. Negative markers included BCL6, CD10, MEF2B, MAL, CD273, CD200, and BCL2. ISH for EBER was negative. Variable numbers of T-cells (CD3+) and B-cells (CD20+) were seen in the background.

Flow cytometry showed 46% T-cells (CD4:CD8 - 3:1) without phenotypic aberrancy, 12% polytypic B-cells, and 1% NK-cells.

Cytogenetics

FISH analysis detected IGH::BCL2 (94% nuclei) and MYC (64%) rearrangements. No BCL6 rearrangement was identified.

Molecular Studies

None

Proposed Diagnosis

Mediastinal Gray Zone Lymphoma with IGH::BCL2 and MYC rearrangements (double hit genotype).

Interesting Feature(s)

Although many areas of the lymph node showed findings compatible with CHL, NS subtype, multiple foci displayed morphologic and immunphenotypic features supportive of mediastinal gray zone lymphoma. The occurrence of IGH::BCL2 and MYC rearrangements in mediastinal gray zone lymphoma is unusual. BCL2 rearrangements have

been described in a small fraction of primary mediastinal large B-cell lymphomas (PMBLs) and rare cases of genetic double (BCL2 or BCL6 and MYC) or triple (BCL2, BCL6, and MYC) hit PMBLs have been reported, at times representing relapsed disease. CHL transformed from follicular lymphoma can also harbor an IGH:BCL2 rearrangement. There was no clinical evidence of follicular lymphoma in our patient.

Panel Diagnosis: Composite Lymphoma with area of classic Hodgkin lymphoma and area of LBCL with double hit BCL2/MYC

LYMPHOMA SESSION II | B-cell lymphomas with prominent histiocytes, e.g. T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), THRLBCL-like lymphomas including Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL) and nodular lymphocyte -predominant Hodgkin lymphoma/ nodular lymphocyte predominant B-cell lymphoma (NLPHL/NLPBL) pattern E, other aggressive or small B-cell lymphomas with granulomatous reaction

EA4HP26-LYWS-7	Burkitt lymphoma with florid granulomatous reaction
EA4HP26-LYWS-12	CMV-triggered Rosai-Dorfman(-like) disease, clinically mimicking transformation in an LPL patient
EA4HP26-LYWS-50	EBV positive lymphoproliferation in an oral ulcer
EA4HP26-LYWS-57	Granulomatous reaction in "slow-growing" Burkitt lymphoma
EA4HP26-LYWS-60	NLPHL or THRLBCL
EA4HP26-LYWS-62	Floral variant of follicular lymphoma mimicking Hodgkin lymphoma.
EA4HP26-LYWS-70	Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma with BM involvement mimicking T-cell lymphoma
EA4HP26-LYWS-77	T-cell/Histiocyte-Rich Large B-cell Lymphoma with Novel Inv/t(16;16)(p12.1;q22.1)/IL21R::CDH1 and Multiple Low-Level Mutations
EA4HP26-LYWS-85	T-Cell/Histiocyte-Rich Large B-Cell Lymphoma-Like Transformation of Nodular Lymphocyte-Predominant B-Cell/Hodgkin Lymphoma With an Associated Clonal T-Cell Population
EA4HP26-LYWS-91	Composite nodal marginal zone lymphoma and histiocytic/dendritic cell neoplasm (favor interdigitating dendritic cell sarcoma)
EA4HP26-LYWS-101	Follicular lymphoma with exuberant T-cells and histiocytes
EA4HP26-LYWS-103	Lymphomatoid Granulomatosis with B- and T-cell clones
EA4HP26-LYWS-108	EBV-positive Diffuse Large B-cell Lymphoma and Nodular Lymphocyte Predominant Hodgkin Lymphoma
EA4HP26-LYWS-122	The borderline between EBV+NLPBL and EBV+DLBCL, NOS in young patients
EA4HP26-LYWS-133	Nodular lymphocyte-predominant Hodgkin lymphoma with prevalent pattern E and minor pattern D in an adolescent
EA4HP26-LYWS-134	Relapsing T-cell histiocyte rich B-cell lymphoproliferation – NLPHL pattern E or THRLBCL?
EA4HP26-LYWS-135	Case of phenotypic overlap between nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma
EA4HP26-LYWS-136	Epstein-Barr virus positive diffuse large B-cell lymphoma
EA4HP26-LYWS-140	When Metastatic Carcinoma Is Not the Answer: EBV-Positive Diffuse Large B-Cell Lymphoma With Granulomatous Features in the Liver
EA4HP26-LYWS-144	B-Cell Lymphoma with Reed–Sternberg–Like Cells and a Prominent Histiocytic Background: A Diagnostic Challenge
EA4HP26-LYWS-145	Histiocyte-rich Germinal Center-Type Diffuse Large B-cell Lymphoma Arising in the Setting of Common Variable Immunodeficiency

EA4HP26-LYWS-146	Splenic marginal zone lymphoma with extensive sarcoid-like granulomatous inflammation
EA4HP26-LYWS-151	Nodular lymphocyte -predominant Hodgkin lymphoma/ nodular lymphocyte predominant B-cell lymphoma (NLPHL/NLPBL) pattern E with an aggressive clinical course and complications of hemophagocytic lymphohistiocytosis (HLH)
EA4HP26-LYWS-171	Follicular lymphoma with prominent histiocytic expansion
EA4HP26-LYWS-173	NLPHL/NLPBL and DLBCL: Composite or transformation?
EA4HP26-LYWS-174	Rapidly Progressive "Sarcoidosis"
EA4HP26-LYWS-187	28-year-old female with 6.3-cm enlarged axillary lymph node
EA4HP26-LYWS-191	Mantle cell lymphoma with florid granulomatous reaction
EA4HP26-LYWS-192	Nodular lymphocyte predominant Hodgkin lymphoma with extensive pattern E
EA4HP26-LYWS-207	T-cell histiocyte rich large B-cell lymphoma with CD30 expression
EA4HP26-LYWS-220	T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
EA4HP26-LYWS-227	Large B-cell lymphoma with a lymphocyte and histiocyte rich microenvironment: a diagnostic dilemma
EA4HP26-LYWS-228	EBV-positive diffuse large B-cell lymphoma, NOS, with T-cell/histiocyte-rich large B-cell lymphoma-like morphology
EA4HP26-LYWS-229	Primary Bone Marrow Presentation of a rare case of T-Cell/Histiocyte-Rich Large B-Cell Lymphoma: A Diagnostic Challenge.
EA4HP26-LYWS-230	T-cell/histiocyte-rich large B-cell lymphoma
EA4HP26-LYWS-240	Histiocyte-rich, EBV-positive diffuse large B-cell lymphoma preceding angioimmunoblastic T-cell lymphoma by 4 years.
EA4HP26-LYWS-243	T-cell/histiocyte-rich large B-cell lymphoma followed by sarcoid-like reaction
EA4HP26-LYWS-246	From Indolent to Aggressive disease: Transformation of Nodular Lymphocyte Predominant Hodgkin Lymphoma to T-Cell/Histiocyte-Rich Large B-Cell Lymphoma
EA4HP26-LYWS-266	EBV-Positive T-Cell/Histiocyte-Rich Large B-Cell Lymphoma in a Lung Transplant Recipient
EA4HP26-LYWS-267	T-cell/Histiocyte Rich Large B-cell Lymphoma in a patient with a remote history of Nodular Lymphocyte Predominate Hodgkin (B-cell) Lymphoma
EA4HP26-LYWS-271	Splenic Marginal Zone Lymphoma with Plasma Cell Differentiation Associated with Crystal Storing Histiocytosis
EA4HP26-LYWS-273	Nodal T follicular helper cell lymphoma vs EBV+ Nodular lymphocyte predominant B-cell lymphoma
EA4HP26-LYWS-275	Nodular Lymphocyte Predominant Hodgkin Lymphoma arising in a patient with immunodeficiency due to germline TACI / TNFRS13B mutation
EA4HP26-LYWS-276	Large cell transformation of follicular lymphoma with a prominent histiocyte rich background
EA4HP26-LYWS-285	Large B-cell lymphoma with a T-cell / histiocyte-rich pattern in a young patient
EA4HP26-LYWS-288	T-cell/histiocyte-rich large B-cell lymphoma with expression of T follicular helper markers.
EA4HP26-LYWS-289	B-cell lymphoma with a T-cell / histiocyte-rich pattern with hemophagocytosis in a pediatric patient

EA4HP26-LYWS-296	Nodal marginal zone lymphoma with an epithelioid histiocyte-rich pattern mimicking Lennert lymphoma
EA4HP26-LYWS-299	Unraveling NLPHL Fan Pattern C→E (THRLBCL-like) Progression with Abundant Epithelioid Histiocytes (Granuloma-like reaction): Diagnostic Pitfalls and Pattern-Stratified Therapy Needs
EA4HP26-LYWS-300	Large B-cell Lymphoma with T-cell/Histiocyte Rich Background
EA4HP26-LYWS-308	EBV positive Diffuse Large B cell lymphoma morphologically resembling T-cell/histiocyte-rich large B-cell lymphoma
EA4HP26-LYWS-313	THRBCL with Markedly Atypical T-cells
EA4HP26-LYWS-314	THRBCL with Paraneoplastic Symptoms Mimicking RA
EA4HP26-LYWS-318	A case of Epstein-Barr virus positive diffuse large B-cell lymphoma
EA4HP26-LYWS-321	Histiocytic-rich EBV-positive B-cell neoplasm in a limited gastric biopsy
EA4HP26-LYWS-322	T-cell/histiocyte-rich large B-cell lymphoma of epidural soft tissue developing in a treated diffuse large B-cell lymphoma
EA4HP26-LYWS-324	When Histiocytes Hide the Lymphoma: A Granulomatous Variant of High-Grade Follicular Lymphoma
EA4HP26-LYWS-325	EBV-associated transformation of follicular lymphoma
EA4HP26-LYWS-326	EBV-associated Burkitt lymphoma with prominent granulomatous reaction
EA4HP26-LYWS-333	"Complex Cytogenetic Aggressive B-Cell Lymphoma Confined to Bone Marrow Presenting as HLH-Like Syndrome"
EA4HP26-LYWS-359	EBV-positive large B cell proliferation in a TFH-rich background
EA4HP26-LYWS-361	Nodular Lymphocyte Predominant Hodgkin Lymphoma, pattern E with secondary EBV infection
EA4HP26-LYWS-363	Composite Lymphoma of EBV-Positive Diffuse and Follicular Large B-cell Lymphoma and Mantle Cell Lymphoma with Increased Epithelioid Histiocytes
EA4HP26-LYWS-366	Bridging Immune Dysregulation and Malignancy: B-Cell Lymphoma in the Context of Immunodeficiency
EA4HP26-LYWS-373	EBV+ Diffuse large B-cell lymphoma with a T-cell/histiocyte-rich background.
EA4HP26-LYWS-378	EBV-positive Large B-cell lymphoma incidentally identified in an amputated specimen
EA4HP26-LYWS-379	Unusual Late Relapse with T-cell/Histiocyte-rich Large B-cell lymphoma (THRLBL)-like Transformation Thirty years after treated Nodular Lymphocyte-Predominant Hodgkin Lymphoma
EA4HP26-LYWS-381	A challenging diagnosis between a nodular lymphocyte predominant Hodgkin lymphoma (OMS 2022) / nodular lymphocyte predominant B-cell lymphoma (ICC 2022) with CD30 heterogenous expression and altered B-cell program, and a classic Hodgkin lymphoma lymphocyte-rich subtype
EA4HP26-LYWS-396	Marginal zone lymphoma relapse obscured by a histiocytic reactive proliferation
EA4HP26-LYWS-399	CD30-positive NLPHL, pattern D-E with a strong suspicion of transformation to DLBCL.
EA4HP26-LYWS-404	A Case of an EBV Positive Mucocutaneous Ulcer in the Vagina
EA4HP26-LYWS-409	Where Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) meets Classic Hodgkin lymphoma, lymphocyte-rich (CHL-LR) subtype: A Diagnostic Gray-Zone Case
EA4HP26-LYWS-410	T-cell/histiocyte-rich large B-cell lymphoma-like morphology on a core biopsy

EA4HP26-LYWS-413	Nodular lymphocyte predominant Hodgkin lymphoma in an elderly gentleman
EA4HP26-LYWS-414	T-cell/Histiocytes-Rich Large B-cell Lymphoma (THRLBCL)
EA4HP26-LYWS-426	Crystal Storing Histocytosis Involving Bone Marrow and Leptomeninges Associated with Lymphoplasmacytic Lymphoma/Waldenstrom's macroglobulinemia
EA4HP26-LYWS-438	A 16-Year-Old Male with Mediastinal Mass and Right Axillary/Chest Swelling
EA4HP26-LYWS-439	T-cell/Histiocyte-Rich Large B-cell Lymphoma in Pediatric Patients
EA4HP26-LYWS-442	EBV+ Large B-cell Lymphoma, Post-Transplant for Subcutaneous Panniculitis-Like T-cell Lymphoma
EA4HP26-LYWS-449	TCHRLBCL Inguinal Lymph Node

Burkitt lymphoma with florid granulomatous reaction

Dr. Tamara Pikivaca¹, Dr. Lina Shao², Dr. Anamarija Perry²

¹ University Hospital Centre Zagreb, Pathology and Cytology, Zagreb, Croatia; ² University of Michigan, Pathology, Ann Arbor, USA

Case Description

A 62-year-old man presented with a three-week history of enlarging left neck mass, refractory to antibiotics. The CT scan showed 4.8 x 3.9 x 3.1 cm left neck mass, and excisional biopsy of this mass/lymph node was done. Upon diagnosis of lymphoma, PET staging showed metabolically active bilateral cervical lymphadenopathy with no evidence of lymphoma elsewhere. Bone marrow and cerebrospinal fluid were negative for involvement. The patient received 5 cycles of dose adjusted R-EPOCH (Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin), along with intrathecal methotrexate, achieving a complete remission. After a 7-year follow-up he remained lymphoma free but died at the age of 69 of cholangiocarcinoma.

Biopsy Fixation Details

Formalin-fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph node sections show complete architectural effacement by a prominent non-necrotizing granulomatous reaction with numerous giant cells, as well as a diffuse monotonous atypical lymphoid infiltrate. Lymphoma cells are medium-sized, with round to slightly irregular nuclei, finely clumped chromatin, and small to inconspicuous nucleoli. There are scattered tingible body macrophages, frequent mitoses and apoptosis.

Immunophenotype

The lymphoma cells are positive for CD20, CD10, BCL6, and C-MYC and are negative for BCL2, MUM1, TDT, CD138, and HHV8. Ki-67 is virtually 100%. EBER-ISH is diffusely positive.

Flow cytometry showed a CD10+ B-cell population without definitive surface light chain expression. The lymphoma cells were positive for CD10 (dim), CD19, CD20, CD38, and CD45.

Cytogenetics

Karyotype revealed t(2;8) which is associated with *IGK::MYC* - 46,XY,t(2;8)(p11.2;q24)

FISH was positive for *MYC* rearrangement, and negative for *BCL2* and *BCL6* rearrangements.

Molecular Studies

None

Proposed Diagnosis

Burkitt lymphoma with florid granulomatous reaction

Interesting Feature(s)

This is a rare case of non-endemic Burkitt lymphoma with florid granulomatous reaction, that is obscuring large areas of lymphoma cells. Burkitt lymphoma can rarely show true granulomatous reaction. These cases were reported to have a favorable prognosis and occasional spontaneous regression. Our patient had disease localized to the neck and was cured after standard chemoimmunotherapy.

References:

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Panel Diagnosis: BL with granulomatous reaction

EA4HP26-LYWS-12

CMV-triggered Rosai-Dorfman(-like) disease, clinically mimicking transformation in an LPL patient

Prof. Thomas Tousseyn^{1,2}

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Case Description

An 82-year-old man presented in August 2025 with a generalized rash, weight loss, night sweats, diffuse lymphadenopathy, and warm AIHA. Initial work-up incl. bone marrow investigation revealed an indolent B-cell lymphoma harboring a MYD88 mutation. Flow cytometry (CD200+), supported the diagnosis of lymphoplasmacytic lymphoma. Serum studies revealed a slightly increased IgM level (24.10 g/L). A PET/CT performed demonstrated multiple discrete hypermetabolic lymphadenopathies. Given the presence of AIHA, treatment was initiated consisting of rituximab, dexamethasone and cyclophosphamide.

Shortly after treatment initiation, the patient developed persistent fever and ongoing night sweats. A repeat PET/CT showed progressive disease, with multiple moderately to strongly hypermetabolic lymphadenopathies and hypermetabolic bone marrow involvement, raising concern for large-cell transformation.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

Y

Details of Microscopic Findings

Lymph node tissue diffusely disturbed by an expansile lymphoproliferative process composed of small to medium-sized lymphoid cells with plasmacytoid morphology and plasma cells. No arguments for large cell transformation or necrosis. Focally, prominent iron deposition is observed.

In one of the sections, there is a focal proliferation of histiocytes with emperipolesis.

Immunophenotype

The lymphoproliferation expresses CD20, IgM and BCL2, and lacks BCL6, CD10, Cyclin D1, LEF1, SOX11, CD23. Plasmacytic differentiation is illustrated by MUM1 (not by CD138) and express IgM κ.

However a focal aggregate of CD138+ IgG λ light-chain restricted plasma cells are present within the histiocytic area. No IgG4+ cells.

The histiocytes co-express CD68/CD163/S100 and show emperipolesis.

The overall Ki67 is low (<5%), but increased in the histiocytic focus.

Cytogenetics

ongoing

Molecular Studies

MYD88 c.794T>C (p.(L265P)) mutation

Monoclonal IgH/K

CMV viral load: 3800 copies

NGS for RDD: ongoing

Proposed Diagnosis

Focal RDD-like histiocytic proliferation with a small aggregate of IgG λ -restricted plasma cells present in a lymph node involved by lymphoplasmatic lymphoma (IgM κ), triggered by CMV infection(?).

Clinically mimicking large cell transformation, but B-symptoms resolved and viral load dropped after valganciclovir treatment

Interesting Feature(s)

Rosai Dorfman disease as a clinical mimic of large cell transformation is rare.

Focal RDD-like histiocytic reaction have been described to occur alongside or intermingled with lymphoma. They are usually interpreted as an incidental, localized (paraneoplastic) proliferative histiocytic lesion rather than a true transformation, particularly if no gene mutations are detected (Garces et al. Modern Pathology (2019) 32:16–2). It is considered an immune-mediated ‘paraneoplastic’ histiocytic response

Is the RDD in this case triggered by CMV infection, as clinically the B-symptoms resolved after valganciclovir treatment?

Individual case reports of true Rosai-Dorfman disease developing after viral infections, for example in association with COVID-19 infection (Gogia et al. Front Med 2022 Dec 19;9:1073767) or vaccination — which suggests that immune dysregulation triggered by a viral infection can provoke RDD histiocytic proliferation in susceptible individuals. However, we found no reports on CMV-triggered “Rosai-Dorfman-like” histiocytic reactions.

What explains the second monotypic plasma cell population (IgG λ), that is different from the IgM κ LPL lymphoma? Do they represent (1) a true second clonal population or (2) an apparent/“pseudo-clonal” restriction in a reactive microenvironment?

Panel Diagnosis: LPL w/ Rosai Dorfman areas

EA4HP26-LYWS-50

EBV positive lymphoproliferation in an oral ulcer

Dr. Chee Leong Cheng

Singapore General Hospital, Anatomical Pathology, Singapore, Singapore

Case Description

85 years old, Asian, Female. She has a past history of hypertension, raised lipids and hearing loss. She was on follow up with otolaryngology for hearing loss, and subsequently presented with right nasal pain and blocked nose. On examination, the right nasal cavity is narrowed with deviated septum and right vestibule swelling. There is also a 1cm ulcer at right hard palate. CT scan showed lobulated lesion at right nasolabial fold measuring 2.3 x 1.7 x 1.3cm, extending into the right nasal vestibule and abuts the nasal septum. There is no known lung lesion. A biopsy of ulcer at right hard palate was performed and submitted.

Biopsy Fixation Details

10% Neutral Buffered Formalin.

Frozen Tissue Available

No frozen section was performed.

Details of Microscopic Findings

There is a fragment partly covered by stratified squamous epithelium with surface ulceration. The underlying fibroadipose tissue shows patchy angiocentric and possible angiodestructive polymorphous lymphoid infiltrate. In some foci, histiocytes (including some epithelioid forms) are prominent, accompanied by necrosis. There are loose clusters and aggregates of atypical large cells ranging from immunoblast-like to Hodgkin-like. Special stains are negative for acid fast bacilli (Ziehl-Neelsen) and fungal organisms (Grocott-Gomori methenamine silver).

Immunophenotype

The atypical medium-to-large cells are B-lymphoid cells that are positive for CD20, CD79a and PAX5, with high proliferation index (Ki-67), and show substantial positivity for CD30 and EBER. There are interspersed (mostly dispersed, albeit numerous) CD3 positive T-lymphocytes which are mostly small in size. The atypical B-lymphoid cell are also MUM1 positive, bcl-2 weak positive, cyclin D1 negative and TdT negative. There are no CD21 immunoreactive follicular dendritic meshworks discerned.

Cytogenetics

No cytogenetics tests were performed.

Molecular Studies

No molecular studies were performed.

Proposed Diagnosis

Atypical Epstein-Barr Virus (EBV) positive B-Lymphoproliferative process, favour EBV positive polymorphic B-cell lymphoproliferative disorder (ICC). EBV positive diffuse large B-cell lymphoma not excluded.

Interesting Feature(s)

- Pitfall: This case could be mistaken as a reactive ulceration with inflammation and immunoblastic reaction unless careful attention is paid to scrutinize the cytomorphology of the lymphoid infiltrate.
- Differential Diagnosis includes the below
 - EBV positive mucocutaneous ulcer (EBV MCU)
 - This can be challenging to completely exclude in the current specimen, but the lack of a well-defined border with dense band-like lymphoid infiltrate at the base of the ulcer, together with a nasal mass that can be closely related to the current specimen makes this case unusual for EBV MCU.
 - EBV positive diffuse large B-cell lymphoma (EBV+ DLBCL)
 - There are features suspicious for incipient EBV + DLBCL in some foci in this specimen
 - Lymphomatoid granulomatosis (LYG)
 - The angiocentric and possible angiodestructive infiltrate accompanying foci of necrosis suggest this possibility, but the lack of lung lesion does not fit the WHO definition for LYG

Panel Diagnosis: Favor EBV+ DLBCL

EA4HP26-LYWS-57

Granulomatous reaction in "slow-growing" Burkitt lymphoma

PhD/MD Massimo Granai, Dr. Domenico Ferrara, Dr. Raffaella Guazzo, **Prof. Stefano Lazzi**

University of Siena, Medical Biotechnology, Siena, Italy

Case Description

An immunocompetent 68-year-old woman presented with right inguinal lymphadenopathy; blood counts/biochemistry were normal and EBV/CMV serology indicated past exposure (IgG+/IgM-). Seven months later, ultrasound and contrast-enhanced CT revealed widespread subdiaphragmatic lymphadenopathy and a 7 cm pelvic mass, consistent with a lymphoproliferative disorder. Excision of two lymph nodes established a diagnosis of Burkitt lymphoma. PET/CT demonstrated multiple FDG-avid sites predominantly below the diaphragm (Ann Arbor stage II); bone marrow biopsy was negative. Dose-adjusted R-EPOCH was initiated with diagnostic/therapeutic lumbar puncture and intrathecal therapy, followed by three additional prophylactic intrathecal; high-dose methotrexate was planned for CNS prophylaxis at the end of systemic therapy. After two cycles (~2 months), she was clinically well with a complete metabolic response.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded (FFPE).

Frozen Tissue Available

Not available

Details of Microscopic Findings

A prominent non-necrotizing epithelioid granulomatous reaction is seen, including multinucleated giant cells; granulomas are partially intermingled with single or cohesive proliferation of monomorphic medium-sized lymphoid cells with round nuclei, clumped chromatin, multiple small nucleoli, and deeply basophilic cytoplasm. Numerous mitotic figures and focal characteristic "starry-sky" pattern were detected.

Immunophenotype

Pan-B-cell markers positive; CD10+, BCL6+, LMO2-, BCL2-, MUM1/IRF4-, CD5-, Cyclin D1-, TdT-, CD38+, CD44-. MYC protein >90%; Ki-67 >95%. EBER in situ hybridization positive.

Cytogenetics

FISH demonstrated MYC translocation without BCL2 and BCL6 rearrangements.

Molecular Studies

None.

Proposed Diagnosis

Burkitt lymphoma with granulomatous reaction.

Interesting Feature(s)

The present case showed an uncommon clinical course for Burkitt lymphoma. Indeed, Burkitt lymphoma is among the fastest-growing human cancers and typically requires urgent, intensive chemotherapy. In this immunocompetent patient, treatment was initiated several months after the onset of generalized lymphadenopathy, yet a complete metabolic response was ultimately achieved. Histology disclosed florid non-necrotizing epithelioid granulomas admixed with tumor cells. Emerging multiplex immunohistochemistry and gene-expression profiling suggest that BL associated with a granulomatous reaction represents a biologically distinct entity, characterized by a pro-inflammatory (M1/Th1-skewed) tumor microenvironment associated with favorable clinical behavior and occasional spontaneous regression. We hypothesize that such an inflammatory milieu may have tempered pre-treatment dynamics and contributed to enhanced chemosensitivity. This could open the way to innovative therapeutic strategies. The extensive granulomatous response is also a diagnostic pitfall obscuring the tumor cells.

Panel Diagnosis: BL with granulomatous reaction

EA4HP26-LYWS-60

NLPHL or THRLBCL

Dr. Ljiljana Vrbanus, Prof. Birgitta Sander, PhD/MD Monika Klimkowska, PhD/MD Sulaf A. Own, Prof. Anna Porwit

Karolinska University Hospital, Clinical pathology/hematopathology, Stockholm, Sweden

Case Description

January 2025:

-77-year-old man

-DM type 2, hypertension, hyperlipidemia, prostatic hyperplasia

-fatigue, some night sweats, no fever, no weight loss

-anemia, thrombocytopenia, widespread lymphadenopathy, splenomegaly, no bone marrow involvement

Biopsy Fixation Details

Formalin-Fixed, Paraffin-Embedded

Frozen Tissue Available

N/A

Details of Microscopic Findings

T1692-25 left inguinal node:

- nodular architecture
- mixture of small lymphocytes, single large polymorphic cells, some of them with lobed nuclei and nucleoli
- abundant histiocytes in the background, few plasma cells and some granulocytes
- no clear granulomas or necrotic changes

Immunophenotype**T1692-25 left inguinal lymph node (January)**

- B cells, different sizes, polymorphic, expressing PAX5, CD30, CD45, CD20, CD79a, BOB1, OCT2, Bcl2, weak Bcl6, p53, some CD25, Ki-67=30%
- no CD15, cyclin D1, CD10, IEBER, MUM1, IgD
- uninterpretable kappa and lambda
- CD21, CD23 scanty positive FDC meshwork
- background rich in CD4 T cells and macrophages hardly any plasma cells
- no complete PD1-rosette formation

T5890-25 cervical lymph node (March)

- vaguely nodular architecture
- mixture of B-cells, some scattered large lobed cells positive for CD45, CD20, CD79a, PAX5, BOB1, OCT2, BCL-2, BCL-6, EMA (few), P53 variable
- no sheet-like DLBCL growth
- negative for CD10, CD15, CMV, IEBER, ALK1, IgD, Perforine, Granzyme, GATA3
- CD21, CD23-no follicular dendritic meshwork
- PD1 no obvious rosettes
- low percentage of CD30, mainly small cells
- C-MYC-20%, Ki-67-30%
- CD138 few plasma-cells
- eosinophils not seen
- background rich in histiocytes (no granuloma) and T-lymphocytes (CD3, CD4, ICOS, PD1)

Flow cytometry

- dominance of T cells (70%), CD4/CD8 ratio of 10

B-cell population:

- dominance of CD45+, CD38+, CD19+, CD20+, CD5-, CD10-kappa negative/lambda negative B-cells (3,9%)

Cytogenetics

N/A

Molecular Studies**T1692-25**

PCR analysis: clonal rearrangement of IGHC, minimal IGK products.
Polyclonal TCR configuration.

Proposed Diagnosis

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
T-cell-rich/histiocytic-rich large B-cell lymphoma (THRLBCL)

Interesting Feature(s)

The morphological and immunohistochemical picture shows features of NLPHL in both lymph nodes, but not a completely typical NLPHL picture is shown (nodular areas lacking follicular dendritic networks)

nor a completely typical picture of T-cell/histiocytic large B-cell lymphoma is shown (More diffuse picture T5890-25, without clear nodular structures, no follicular dendritic networks but still admixed remaining small B cells, in the background predominant TFH-type of T-cells).

Considering the advanced stage of the lymphoma according to PET we have agreed that it may be:

" Large B-cell lymphoma with T-cell-rich background and nodules lacking follicular dendritic cell meshwork's: description of an insufficiently recognized variant."

From the article:

"...B-cell lymphomas with features intermediate between NLPHL and THRLBCL to reflect their overlapping clinicopathological features between NLPHL and THRLBCL...Whether these cases represent another histologic variant of NLPHL or an intermediate category..."

PAD: Large B-cell lymphoma that cannot be reliably classified according to the WHO classification of tumors of hematopoietic and lymphoid tissue (years 2017 and 2022).

Nodular lymphocyte predominant B-cell lymphoma (NLPBL) Grade 2? (ICC 2022).

Clinical conclusion: B-cell Lymphoma, high-malignant, unclassified.

R-CHOP 21 six courses (starting May 2025).

PET-CT complete metabolic remission (November 2025).

Panel Diagnosis: NLPB/HL

EA4HP26-LYWS-62

Floral variant of follicular lymphoma mimicking Hodgkin lymphoma.

Dr. Teodora Popa, Dr. Eric D. Hsi, Dr. Rebecca L. King

Mayo Clinic, Hematopathology, Rochester, USA

Case Description

A 59-year-old female was referred to hematology for submental lymphadenopathy. A core needle biopsy demonstrated an atypical lymphoid infiltrate with increased CD30 positivity. An excisional biopsy was subsequently performed.

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

NA

Details of Microscopic Findings

Histologic sections show an abnormal macronodular lymphohistiocytic infiltrate. The nodules have a moth-eaten or scalloped pattern, and consist of predominantly small lymphocytes with irregular contours (centrocytes). Scattered large atypical cells with lobated nuclei, open chromatin, and prominent nucleoli, resembling lymphocyte-predominant (LP) or Reed-Sternberg (RS) cells, are present both within and surrounding the nodules. Epithelioid histiocytes are present and form small granulomas around the nodules.

Immunophenotype

Flow cytometry: B cells are CD10-positive with indeterminate light chain expression.

Immunohistochemistry: CD20 shows nodules of B cells surrounded by CD3-positive T cells. The nodules represent follicles with fragmented germinal centers highlighted by CD10, BCL6, and MEF2B, which are positive for BCL2. CD30 stains a subset of variably sized cells within the follicles. IgD shows surrounding mantle zones, further highlighting the floral pattern, and CD21 stains follicular dendritic meshworks in association with the follicles. On close inspection, the large lobulated cells, which initially were concerning for LP or RS cells, express CD30 (strong),

CD45, PAX5 (variable), CD19, CD20, CD79a, OCT2, BOB1, BCL6, MEF2B (variable), MUM1 (weak), and BCL2. They are negative for CD15. EBER is negative. Rosetting with PD1 is not seen.

Cytogenetics

FISH is positive for a *BCL2* rearrangement and *IGH* rearrangement (break apart probes, 70%) in both the small centrocytes and large lobulated cells.

Molecular Studies

NA

Proposed Diagnosis

Follicular lymphoma, floral variant, with prominent LP-like cells.

Interesting Feature(s)

This is a rare variant of low-grade follicular lymphoma (FL) that is known to mimic progressive transformation of germinal centers (PTGC), characterized by prominent mantle zones that invaginate irregularly into the follicles, imparting a “floral” appearance. (1) The microenvironment in floral FL contains T cells and epithelioid histiocytes, and raises a challenging differential that pathologists need to be aware of.

Our case was made particularly difficult due to the presence of intermixed large cells resembling LP cells or RS cells, raising the differential diagnosis of nodular lymphocyte predominant B cell/Hodgkin lymphoma (NLP) or lymphocyte rich classic Hodgkin lymphoma (LRCHL). While NLP and floral FL show similar architectural features, it is critical to distinguish these two diseases. Features that refute classification as NLP in this case include the presence of a centrocytic component with a germinal center phenotype and *BCL2* rearrangement (*BCL2*-R). Furthermore, both the small centrocytes and large cells harbored the *BCL2*-R, confirming that this is one process. While FL with concurrent CHL was considered due to the CD30 expression, it was dismissed due to expression of CD45 and CD19 as well as other pan B cell markers in the large cells.

Review of the literature revealed that very rare cases of floral FL have been reported to contain LP-like cells, mimicking NLP/HL. (2) To our knowledge, this is the first such case to document the *BCL2*-R in these cells.

References:

1. Goates, JJ, *et al.* Floral Variant of Follicular Lymphoma. *Am J Surg Pathol.* 1994;18(1):37-47.
2. Kojima M, *et al.* Histological variety of floral variant of follicular lymphoma. *APMIS.* 2006 Sep;114(9):626-3.

Panel Diagnosis: FL, floral variant

EA4HP26-LYWS-70

Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma with BM involvement mimicking T-cell lymphoma

Prof. Kung-Chao Chang

National Cheng Kung University Hospital, Department of Pathology, Tainan, Taiwan

Case Description

A 53-year-old man suffered from left upper quadrant (LUQ) pain for one more months. The initial work-up revealed splenomegaly (27 cm) and pancytopenia (WBC, 1300/ μ L; Hb, 10.6 g/dL; Platelet, 26k/ μ L), accompanied by body weight loss, sweating, and fever. Lab data showed elevated AST (134 U/L), ALT (117 U/L), Alk-P (406 U/L), BIL-T (2.3 mg/dL), and BIL-D (1.8 mg/dL) levels. Both bone marrow and peripheral blood showed no evidence of clonal T cells by flow cytometry, but infiltration of atypical T cells was noted in the bone marrow biopsy, favoring T-cell lymphoma involvement. The patient underwent DA-EPOCH chemotherapy, which initially got partial response but splenomegaly and pancytopenia reappeared. Splenectomy was subsequently done.

Biopsy Fixation Details

The resected spleen was fixed in neutral formalin for 10 hours and then paraffin-embedded. H&E sections and immunohistochemical staining were performed by the standard protocol.

Frozen Tissue Available

Frozen tissue was not available.

Details of Microscopic Findings

Sections showed effacement of the splenic architecture by an infiltrate composed predominantly of small lymphocytes and histiocytes arranged in a nodular pattern. Scattered among the infiltrate were large atypical cells with vesicular chromatin, prominent nucleoli, and moderate abundant cytoplasm.

Immunophenotype

Immunohistochemically, the large atypical cells were positive for CD20, BCL2, BCL6 (focal), MUM1 (focal) and c-MYC (focal), and negative for CD3 and CD10 with a Ki-67 index of 90%. CD30- and EMA-positive cells were sparse. EBER in situ hybridization was negative. The stromal cells in the nodules were negative for CD21. CD68 highlighted intermixed histiocytes.

Cytogenetics

Not available.

Molecular Studies

Pending

Proposed Diagnosis

Splenic micronodular T-cell/histiocyte-rich large B-cell lymphoma with BM involvement

Interesting Feature(s)

The initial BM biopsy showed some patchy infiltrates composed predominantly of small angulated lymphocytes and histiocytes intermixed with a few large cells. The majority of lymphocytes were CD3-positive and CD20- negative. The abundance of T cells may lead to erroneous diagnosis of T-cell lymphoma.

Difficulties may arise if the marrow is involved and a marrow trephine is examined without the knowledge of the splenic histology, as was the case in the majority of cases presented in the Dogan's paper (Am J Surg Pathol 2003;27(7): 903–911).

Bone marrow aspirate and flow immunophenotyping are unlikely to be helpful, and accurate diagnosis may indeed be very difficult without a splenectomy. The only helpful feature would be identification of large atypical B cells within the predominantly small lymphocytic infiltrate.

Panel Diagnosis: THRLBCL

EA4HP26-LYWS-77

T-cell/Histiocyte-Rich Large B-cell Lymphoma with Novel Inv/t(16;16)(p12.1;q22.1)/IL21R::CDH1 and Multiple Low-Level Mutations

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Case Description

A 68-year-old obese male presented with back pain in November 2020. He had psoriasis with psoriatic arthritis & was on methotrexate and apremilast (a phosphodiesterase 4 inhibitor). He had also received adalimumab (a TNF inhibitor) for many years. PET/CT scan showed hypermetabolic activity in the bone marrow of axial & appendicular

skeleton, right axillary lymph nodes (LNs) & spleen. He had palpable right axillary lymphadenopathy, no palpable hepatosplenomegaly, no B symptoms, normal CBC, & normal serum LDH. Right axillary LN-mass was excised & submitted fresh. The LNs measured from 3.5 to 7.8 cm, were firm & had whitish homogenous cut surface. A piece of a LN was submitted for flow cytometry & the rest of the tissue was fixed in 10% NBF. Treatment (4 R-EPOCH cycles & 3 intrathecal methotrexate cycles followed by 2 R-CHOP cycles) was given following THRLBCL diagnosis, Stage IV. PET/CT has remained normal for 5 years after treatment.

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

Not available

Details of Microscopic Findings

H & E sections show complete effacement of architecture by a diffuse infiltrate of small lymphocytes, bland histiocytes & a few (~10%) scattered large lymphoid cells. Large lymphoid cells show high NC ratio, variably irregular nuclear contours, slightly condensed chromatin & prominent nucleoli.

Immunophenotype

Flow Cytometry: 11% polytypic CD20+ cells; 87% CD3+ cells without loss of pan-T cell antigen or antigen aberrancy & with 1:1 CD4:CD8 ratio. **Immunohistochemistry:** Large lymphoid cells show positivity for CD45, CD20, CD23, CD79a, PAX5, OCT2, BOB1, BCL6, MUM1 (subset), MYC, E-Cadherin, & Ki67 (~80%) & negativity for EBV-LMP1, BCL2, CD10, CD5, & CD138. Most of small lymphocytes are T cells with expression of CD2, CD3, CD5, CD7, CD8, GATA3 (subset), TBX21 (subset), granzyme B (big subset), TIA-1 (smaller subset), perforin (tiny subset), BCL2, weak sCD20, MUM1 (subset), & showing slightly more CD8+ cells than CD4+ cells. Small subset of CD57+, ICOS-1+, CXCL13+ & PD1+ cells, without any rosettes around large B cells, are also present. A small subset of PD-L1+ small T cells and a few CD56+ dendritic cells also seen. Numerous histiocytes stain for CD68 & CD163.

Cytogenetics

Not done

Molecular Studies

In situ Hybridization: Large cells are kappa mRNA+ (monotypic) & EBER-ve.

FISH for aggressive B-cell lymphoma: No abnormality.

DNA & RNA NGS: Low level mutations detected in *LRP1B*, *HGF*, *SOCS1* (11 mutations), *ATM*, *AKT3*, *DDX41*, *BCORL1*, *NFKB1A*, *IRF8*, *KMT2C*, & *TP53* genes; B-cell oligoclonality detected; Inv/t(16;16)(p12.1;q22.1) *IL21R::CDH1* fusion mRNA detected.

Proposed Diagnosis

T-cell/Histiocyte-Rich Large B-cell Lymphoma with Novel Inv/t(16;16)(p12.1;q22.1)/*IL21R::CDH1* and Multiple Low-Level Mutations

Interesting Feature(s)

1. History of psoriasis & psoriatic arthritis and adalimumab, methotrexate & apremilast therapy. THRLBCL has been reported to occur in association with psoriasis and these treatments.
2. *IL21R::CDH1* fusion could be responsible for E-cadherin expression in the large B cells.
3. IL21-SOCS1 axis involvement due to *IL21R::CDH1* & multiple *SOCS1* mutations could be responsible for T cell/Histiocyte richness.
4. Following features could be responsible for low number of tumor cells (large B cells) and good prognosis: (I) Activated cytotoxic phenotype of T cells (strong granzyme B expression) mounting very effective host anti-tumor response. (II) CD20-positive T cells playing an anti-cancer role. (III) Lack of BCL2 in large B cells causing increased large B-cell apoptosis. (IV) CD56-positive dendritic cells killing tumor cells directly & via cytotoxic CD8+ T cells.

Panel Diagnosis: THRLBCL

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma-Like Transformation of Nodular Lymphocyte-Predominant B-Cell/Hodgkin Lymphoma With an Associated Clonal T-Cell Population

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Franziska Otto, Prof. Falko Fend

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Case Description

A 46-year-old woman presented with axillary lymphadenopathy and a 10-cm soft tissue mass on the right chest wall. Core needle biopsies were obtained from the chest wall mass (submitted) and a left axillary lymph node (LN). Staging investigations are ongoing.

Biopsy Fixation Details

Formalin fixation.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

The chest wall biopsy revealed a diffuse to faintly nodular infiltrate of predominantly small- to medium-sized lymphocytes, some with cytological atypia, variably abundant histiocytes, occasionally forming granulomas, and large atypical cells with enlarged, sometimes lobulated nuclei, prominent nucleoli, and abundant pale cytoplasm. These cells showed a heterogeneous distribution, being scattered in some areas and forming clusters and small sheets in others. Necrosis was also observed. The axillary LN was infiltrated as well, although here the atypical cells were loosely scattered among a vaguely nodular background of small- to medium-sized lymphocytes, without an increase in histiocytes or necrosis.

Immunophenotype

The large atypical cells in the chest wall biopsy showed strong expression of CD20, PAX5, OCT2, and BCL6, whereas EMA and BCL2 were partially positive. CD30, CD15, CD10, IgD, and EBER were negative. Small B cells were almost completely absent. PU.1 highlighted the histiocytes, which were especially prominent in areas rich in atypical B cells. These areas also showed markedly increased proliferation (MIB-1). CD2, CD3, CD5, and CD7 highlighted abundant T cells, some enlarged and/or atypical. Notably, CD5 expression was diminished in a subset of T cells, and CD7 was weak overall. CD8- and TIA1-positive T cells were more abundant in areas rich in atypical B cells and histiocytes, whereas CD4 and PD1 showed the opposite distribution, without prominent rosette formation. CD21 and CD23 revealed an absence of follicular dendritic cell (FDC) meshworks. In contrast, the axillary LN showed nodules of small B cells with FDC meshworks and a prominent extranodular distribution of atypical B cells, embedded in a background rich in PD1-positive T cells showing frequent rosette formation around them.

Cytogenetics

N/A.

Molecular Studies

BIOMED-2 IGH clonality analysis of the chest wall biopsy showed clonal products of 246 bp and 275 bp (FR2). T-cell receptor (TCR) beta clonality analysis also showed clonal products of 257 bp (Tube A) and 195 bp (Tube C). NGS of 93 genes frequently altered in lymphoma did not reveal pathogenic mutations.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma-like transformation of nodular lymphocyte-predominant B-cell/Hodgkin lymphoma (NLPBL/NLPHL) with an associated clonal T-cell population.

Interesting Feature(s)

This case highlights the histological spectrum of NLPBL/NLPHL and exemplifies its transformation into an aggressive lymphoma reminiscent of T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL). THRLBCL-like transformation, as initially described by Hartmann *et al.* (BMC Cancer 2014), is characterized by clusters or small sheets of blasts accounting for >10% of cells in a T-cell/histiocyte-rich background, representing a morphologic overlap between THRLBCL and conventional diffuse large B-cell lymphoma. Furthermore, the atypia of a subset of the T cells, together with the clonal TCR rearrangement, raised concerns for peripheral T-cell lymphoma (PTCL). While atypical T-cell proliferations are recognized in NLPBL/NLPHL, they have so far been reported as polyclonal (Sohani *et al.*, Am J Surg Pathol 2011). Thus, only the absence of typical mutations in the NGS analysis confidently excluded a concomitant PTCL.

Panel Diagnosis: NLPB/HL with atypical T-cell population

EA4HP26-LYWS-91

Composite nodal marginal zone lymphoma and histiocytic/dendritic cell neoplasm (favor interdigitating dendritic cell sarcoma)

Dr. Yeseul Kim¹, Dr. Taesung Jeon²

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Case Description

A 65-year-old woman with a history of hypertension and no other significant underlying disease was diagnosed with left breast cancer by needle biopsy at an outside hospital in August 2025 (left breast, 2 o'clock and 9 o'clock positions) and was referred to our institution for surgical management. During preoperative work-up, multiple enlarged right axillary lymph nodes were identified. Metastatic carcinoma was initially suspected, and a core needle biopsy was performed. The biopsy demonstrated marked histiocytic proliferation with infiltration by atypical B cells, prompting an excisional biopsy for definitive diagnosis.

Biopsy Fixation Details

Formalin fixation (3.7% formaldehyde) for 24 hours.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

- Histologic examination shows a lymph node with a thickened capsule and near-complete architectural effacement. There is geographic infiltration by histiocytes, accompanied by a diffuse infiltrate of B cells throughout the node. Germinal centers and follicles were barely identifiable.
- A subset of the neoplastic B cells shows monocytoid morphology with pale-staining cytoplasm.
- The histiocytic population displays indistinct cell borders and ranges from epithelioid to spindle morphology, forming fascicles and sheet-like growth patterns. The cells have abundant eosinophilic cytoplasm and irregular nuclear contours; multinucleated forms are occasionally present. Mitotic activity is approximately 7 per 2 mm².

Immunophenotype

- B-cell component: CD20 positive; CD10 negative; BCL6 negative; BCL2 positive; MUM1 negative, Ki-67 low.
- Histiocytic/dendritic cell component: CD163 positive; S-100 positive; BRAF negative; CD1a negative; Cyclin D1 focal positive, Ki-67 increased.
- Additional findings: CD3 negative; CD5 negative; CD8 negative; c-MYC negative; CD30 negative. CD21 highlights proliferation/expansion of follicular dendritic cell meshworks.

- EBV: EBER in situ hybridization negative.

Cytogenetics

Not performed

Molecular Studies

- IGH gene rearrangement: positive.
- TCR- β gene rearrangement: negative.
- TCR- γ gene rearrangement: negative.

Proposed Diagnosis

Composite nodal marginal zone lymphoma and histiocytic/dendritic cell neoplasm (favor interdigitating dendritic cell sarcoma)

Interesting Feature(s)

This case shows an intimate admixture of nodal marginal zone lymphoma and a diffuse proliferation consistent with interdigitating dendritic cell sarcoma, rather than two spatially separate (“collision”) lesions. The findings raise the question of whether these two components could be clonally related (e.g., arising from a shared hematopoietic precursor/clone) versus representing a secondary neoplasm developing in the setting of an underlying B-cell lymphoma.

Panel Diagnosis: PICTURES NOT SENT; NOT DISCUSSED

EA4HP26-LYWS-101

Follicular lymphoma with exuberant T-cells and histiocytes

Dr. Kenn Chen¹, Dr. Ritika Walia³, Dr. Angela Zou¹, Dr. Elisa Lin¹, Dr. Yanna Ding¹, Dr. Jason Love¹, Dr. Kikkeri Naresh^{2,1}, Dr. Alireza Torabi¹, **Dr. Xueyan Chen**^{2,1}

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Case Description

A 58-year-old male with a history of hypertension, asthma, and GERD presented with incidentally noted left cervical lymphadenopathy, with suspicion for lymphoma.

Ultrasound demonstrated abnormal enlargement of palpable left upper cervical chain lymph nodes. An excisional biopsy of left level 2 lymph node was performed.

CBC, comprehensive metabolic panel, LDH, and ESR were unremarkable.

PET/CT performed after biopsy showed foci of increased uptake along the excisional biopsy tract, which may be associated with recent biopsy procedures. No additional abnormal uptake was identified in the head, neck, chest, or abdomen.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

The H&E stained lymph node sections show complete architectural effacement by a vaguely nodular and diffuse infiltrate of small to intermediate sized cells with clumped chromatin, and scattered larger lymphoid cells with vesicular chromatin and variable amounts of cytoplasm, admixed with plasma cells and abundant histiocytes.

Immunophenotype

IHC: CD20 and PAX5 highlight disrupted B-cell follicles and interfollicular expanded B cells coexpressing BCL6, CD10, MEF2B, and HGAL, with variable BCL2, MUM1, and MNDA. B cells within the follicles show weak kappa light chain expression. CD21 highlights scattered, disrupted follicular dendritic cell meshworks. The Ki-67 proliferation rate is ~70% in the follicles and 30-40% in the rest of the infiltrate.

CD3 highlights a diffuse infiltrate of T cells with normal expression of CD5 and CD7, mostly of CD4+ cells. The histiocytes are positive for CD68, CD43, lysozyme (weak), and CD163 (subset) and negative for D21, CD23, and CD35. EBER by ISH shows a small subset of scattered positive cells in a patchy distribution.

Flow cytometry revealed 4-5% surface light chain-negative B cells (20-25% of the B cells) among the WBCs, and no significant abnormal T or NK cell populations.

Cytogenetics

FISH studies revealed rearrangement of *BCL6* in 43% of the cells and no rearrangement of *BCL2*.

Molecular Studies

PCR:

CLONAL IG gene rearrangement.

POLYCLONAL TCR gamma gene rearrangement.

NGS panel:

MAP2K1 (p.Cys121Ser, NM_002755.4:c.361T>A, VAF 25%)

XPO1 (p.Glu571Lys, NM_003400.4:c.1711G>A, VAF 13%)

Proposed Diagnosis

Follicular lymphoma with marginal zone differentiation

Interesting Feature(s)

-The combined findings support a diagnosis of follicular lymphoma with marginal zone differentiation, with unusual morphologic features including an exuberant T-cell and histiocyte infiltrate and scattered EBER-positive cells. The unusual microenvironment partially obscures the architecture of the underlying B-cell neoplasm, expanding the differential diagnosis to include entities characterized by a dominant T-cell/histiocyte background, e.g., T-cell/histiocyte-rich large B-cell lymphoma, peripheral T-cell lymphoma NOS with abundant histiocytes (Lennert lymphoma).

-The histiocytic proliferation along with MAP2K1 mutation and cyclin D1 expression raised consideration of a non-Langerhans histiocytosis spectrum disorder; however, MAPK-pathway alterations occur across several histiocytic and B-cell neoplasm subtypes, and the absence of defining clinicopathologic features of Rosai-Dorfman disease, Erdheim-Chester disease, or juvenile xanthogranuloma argues against a diagnosis of histiocytoses.

-In follicular lymphoma, EBV positivity is uncommon and is usually reported in immunocompromised patients. In this case, the relatively small number of EBER+ cells with patchy distribution supports the interpretation as likely bystander EBER+ cells rather than EBV-positive FL.

Panel Diagnosis: Favor FL, BCL2R(-), increased histiocytes and scattered EBV+

EA4HP26-LYWS-103

Lymphomatoid Granulomatosis with B- and T-cell clones

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Case Description

A 38-year-old male with no known past medical history presents to the emergency department with a chief complaint of progressively worsening productive cough, fatigue, and generalized weakness over the past three months. He reports associated night sweats and decreased appetite. The patient has a history of occasional tobacco use and a 10-year history of cocaine use. He has been employed as a painter for the past 8 years.

Chest X-ray: Extensive bilateral pulmonary nodules

Infectious Work up

Mycobacterium tuberculosis complex by PCR; lower respiratory tract sputum-induced: Not Detected.

HIV RNA PCR blood: Negative

Bacterial and Fungal Cultures: Negative

Biopsy Fixation Details

Right and Left Lung; upper lobe biopsies were received in formalin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Histologic sections of biopsies from the right and left lungs reveal multiple vaguely nodular aggregates composed of a polymorphous lymphoid infiltrate with histiocytes and plasma cells. The interspersed intermediate- to large-sized lymphoid cells are characterized by a high nuclear-to-cytoplasmic (N/C) ratio, irregular nuclear contours, and prominent nucleoli. Focal areas of angioinvasion and fibrinoid necrosis of small blood vessels are also identified.

Immunophenotype

Lymphoma cells are positive for CD19, CD20, PAX5, BCL2 (subset), BCL6, MUM1, CD30 (subset of large cells), c-MYC, and EBV EBER, LMP1, and EBNA2 (latency pattern II). The Ki-67 proliferation index is approximately 70%.

The lymphoma cells are negative for CD3, CD10, and BCL1.

Numerous small T-lymphocytes, positive for CD3

IHC for Mycobacterium is negative.

Cytogenetics

Not performed

Molecular Studies

Positive for CLONAL IgH rearrangement

Positive for T-cell gene rearrangement at the TRG locus

Proposed Diagnosis

Lymphomatoid Granulomatosis (LYG), Grade 2

Interesting Feature(s)

LYG is a rare EBV-driven B-cell lymphoma seen in immunocompetent individuals. It is characterized by an angiocentric and angiodestructive pattern of infiltration and typically involves the lungs bilaterally. The histology is notable for a polymorphous cellular infiltrate comprising atypical B cells, numerous T cells, and plasma cells. EBV infection, particularly in the B cells, plays a key role in the pathogenesis. Lymph node and bone marrow involvement are uncommon. Because the disease can progress to high-grade B-cell lymphoma, early detection is essential.

Of interest in this case is the demonstration of both B- and T-cell gene rearrangements

Our case showed 10-15 large EBV-positive cells per high-power field (HPF), consistent with Grade 2 LYG, which is considered intermediate aggressiveness. Grade 2 LYG has a variable clinical course, with the potential to behave indolently or progress to more aggressive disease, including transformation to diffuse large B-cell lymphoma. Close monitoring is important for the timely detection of progression.

Follow up:

Our patient developed inguinal lymphadenopathy that revealed scattered EBV-positive cells without evidence of lymphoma. Flow cytometry of the peripheral blood sample was negative for a monotypic B-cell population.

Panel Diagnosis: LyG

EBV-positive Diffuse Large B-cell Lymphoma and Nodular Lymphocyte Predominant Hodgkin Lymphoma

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Case Description

52-year-old male with history of CLL/SLL diagnosed in 1996, status-post chemotherapy with Fludarabine and Rituxan followed by 6 cycles of R-CHOP and ultimately umbilical cord stem cell transplant in 2001 remained in complete remission until 2017 when surveillance PET-CT scan showed diffuse, hypermetabolic lymphadenopathy concerning for recurrence of lymphoma.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

There is effacement of lymph node architecture by an atypical lymphoid proliferation that manifests in three distinct morphologies. Focal areas of the lymph node demonstrate nodules composed of mostly small lymphocytes with presence of large, atypical cells with vesicular nuclei, prominent nucleoli reminiscent of LP cells. These cells are seen within and outside the nodules. Histiocytic aggregates are also seen within the nodules. In addition, there are extensive areas with a polymorphous appearance composed of abundant histiocytes, lymphocytes and plasma cells. There are abundant interspersed cells with LP cell morphology and Reed-Sternberg cell (and variant) morphology [T-cell/histiocyte rich large B-cell lymphoma (THRLBCL)- like]. Finally, there are areas with sheets of large, atypical cells with LP cell and Reed-Sternberg cell morphology [diffuse large B-cell lymphoma (DLBCL)- like areas]. Areas of necrosis are noted as well as scattered multinucleated giant cells. Clusters of epithelioid histiocytes and granulomatous areas are also noted.

Immunophenotype

The large, atypical cells within the nodular lymphocyte predominant Hodgkin lymphoma like areas are positive for CD20, OCT2 (strong), PAX5 (weak), BCL6 and negative for CD3, and CD15. CD20 and OCT2 demonstrate presence of large LP cells within B cell rich nodular areas; present both within and outside the nodules. CD30 is variably positive the LP cells. The LP cells are rosetted by CD3 and strong PD1 positive cells. CD21 demonstrates expanded meshworks within these nodules.

In addition, within the THRLBCL- like areas as well as within the DLBCL- like areas, CD21 demonstrates loss of meshworks. The large cells in these areas are positive for CD20, PAX5 (weak), BCL6 (variably), CD30 (variably, strong positive in a membranous and golgi zone pattern in some areas), OCT2 and negative for CD15, CD3, and BCL1.

Cytogenetics

No

Molecular Studies

IgH and TCR Gamma gene rearrangements negative

Proposed Diagnosis

1. Diffuse Large B-cell Lymphoma, EBV-positive
2. Nodular Lymphocyte Predominant Hodgkin Lymphoma, EBV-positive

Interesting Feature(s)

Three main distinct morphologies; 1) Nodular lymphocyte predominant Hodgkin like areas 2) T-cell/histiocyte rich large B-cell lymphoma areas and 3) Diffuse large B-cell lymphoma. All morphologic elements appear to be EBV

positive with variations in the extent of positivity. While some of the LP like cells in the Nodular lymphocyte predominant Hodgkin areas are CD30 positive (variably) and PAX5 (dim) this is likely because of concurrent EBV positivity.

Overall, there are several possibilities in this case; 1) The Nodular lymphocyte predominant Hodgkin lymphoma and Diffuse large B cell lymphoma are clonally unrelated composite lymphomas 2) The Diffuse large B-cell lymphoma progressed from the underlying Nodular Lymphocyte Predominant Hodgkin Lymphoma and 3) They represent variations of a post-transplant lymphoproliferative disorder (with polymorphous and monomorphic areas) in concert with Nodular lymphocyte predominant Hodgkin like areas. The last possibility is less likely because of the distant nature of the stem cell transplant (performed in 2001).

Panel Diagnosis: PTLN, NLPB/HL EBV-positive with transformation to EBV+ DLBCL

EA4HP26-LYWS-122

The borderline between EBV+NLPBL and EBV+DLBCL, NOS in young patients

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Case Description

A 9-year-old boy previously healthy presented to the hospital in March 2025 with a history of bilateral cervical, axillary and inguinal lymphadenopathy for three months, asymptomatic. Laboratory results showed IgG for EBV and CMV with negative IgM for both. The patient remained asymptomatic; however, because the cervical lymph nodes increased in size, and excisional biopsy was done in June. A diagnosis of B-cell EBV+ LPD was rendered. A broad immunological work up, including an immunodeficiency mutational panel, did not reveal evidence of immunodeficiency. The patient remained in excellent condition with episodes of fever without evident infection. In November, a second excisional biopsy was performed. PET CT showed high to very high uptake in widespread lymphadenopathy and multiple focal skeletal lesions. MRT confirmed systemic lymphadenopathy most pronounced in the cervical region, numerous skeletal lesions and mild hepatosplenomegaly. The BM biopsy was infiltrated.

Biopsy Fixation Details

4% formalin

Frozen Tissue Available

no

Details of Microscopic Findings

The 1st LN shows mostly effaced architecture with residual enlarged nodules surrounded by diffuse areas. Within and outside the nodules there are large atypical cells including LP, Hodgkin and RS-like cells reminiscent of NLPBL. In the diffuse areas there was a polymorphic infiltrate mimicking THRBCL. The 2nd LN biopsy showed complete effacement of the architecture by a diffuse infiltrate mimicking THRBCL.

BM infiltrated by an atypical lymphoid infiltrate (30-40%).

Immunophenotype

1st biopsy: The large cells CD20+, CD79a+, MEF2B+, OCT2+, PAX5+, BOB1+, CD30 and EMA weak+/-, EBER+ and LMP1+ in small and large cells, EBNA2- (EBV Latency 2). Nodular areas CD23+ FDCs and numerous PD1+ cells forming rosettes. Diffuse areas, polymorphic B-cell infiltrate EBER+ and LMP1+, lack of CD23+FDCs and PD1+ T-cells. T-cells predominantly CD8+, PD-L1+ in large cells.

2nd biopsy: Diffuse effacement by a polymorphic EBER+, LMP1+ and PD-L1+ B-cell infiltrate. Complete lack of

CD23+FDCs and PD1+T-cells

BM infiltrated by a polymorphic EBV+ B-cell infiltrate.

Cytogenetics

N/A

Molecular Studies

PCR B-cells; FR1-3, Kde, IGK polyclonal, IGH DH-JH monoclonal. T-cells polyclonal

Dual K/L ISH: monoclonal kappa.

Proposed Diagnosis

EBV+ DLBCL, NOS with THRBCL-like pattern in a young patient (transformed from EBV+ NLPBL?).

Interesting Feature(s)

This case demonstrates the overlapping features between EBV+NLPBL and EBV+DLBCL, NOS with THRBCL-like pattern in young patients. These two EBV+ subtypes were first described in the 2008 EAHP workshop (PMID: **20309430**), where also the overlapping features of these two diseases was noticed. The existence of EBV+NLPBL was confirmed in subsequent studies (PMID: **24525501**, **24852241**), where it was shown that the EBV infected cells were mainly the LP cells, unlike our case in which there is a wide spectrum of EBV+ B-cells. In a further study of EBV+DLBCL, NOS in young patients (PMID: **25999451**), the THRBCL-like pattern was the most frequently encountered pattern. The authors also noted that most cases have areas reminiscent of NLPBL. The strong PD-L1 expression in tumor cells seems to promote a tolerogenic immune environment. The prognosis of these patients is excellent with overall survival of 87%. The criteria to distinguish EBV+NLPBL and EBV+DLBCL, NOS in young patients are yet to be defined. Whether these cases represent a morphological spectrum of the same disease is a matter of discussion. This might explain why EBV+DLBCL, NOS in young patients has an excellent prognosis when compared to elderly patients.

Panel Diagnosis: EBV+ NLPB/HL, progressed to EBV+ THRLBCL-like

EA4HP26-LYWS-133

Nodular lymphocyte-predominant Hodgkin lymphoma with prevalent pattern E and minor pattern D in an adolescent

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Case Description

Fifteen-year-old boy presented with enlarged cervical and supraclavicular lymph node. Infections were ruled out. Fresh lymph node measuring 60 x 40 x 25 mm was delivered to pathology department; part of lymph node was submitted for flow cytometry. Patient was transferred to paediatric haemato-oncology department of other faculty hospital, further follow up is not available.

Biopsy Fixation Details

buffered formalin

Frozen Tissue Available

NO

Details of Microscopic Findings

Enlarged lymph node with effaced architecture and two different growth areas. Minority of the lymph node had vaguely nodular structure with predominance of small lymphocytes and dispersed larger atypical cells with multilobated nuclei (LP cells) surrounded with small lymphocytic rosettes. Majority of the lymph node showed diffuse

pale areas with proliferation of histiocytes, small to medium sized lymphocytes and similar large neoplastic LP cells. Increased vascularity was seen in some areas.

Immunophenotype

Neoplastic LP cells were positive for LCA, CD20, PAX5, MUM1, bcl6 and showed higher proliferation index in Ki67. They were negative for CD30 and CD15. EBER was negative.

Phenotype of the background showed predominance of CD3/CD4+ T-cells in both areas. T-cells in smaller nodules showed coexpression of PD1 and CD57 and were forming rosettes around LP cells. Follicular dendritic cells (FDC) were retained in nodular areas (CD21 and CD23+). Expression of PD1 and CD57 was diminished in diffuse areas and FDC meshwork was missing. Prominent population in the diffuse areas was composed of histiocytes positive for CD163. Expression of CD8 and TIA was seen in about 30-40 % of T-cells in the background.

Flow cytometry (bone marrow aspirates): performed from native lymph node tissue. Markers evaluated were CD45, CD20, CD19, CD2, CD3, CD4, CD7, CD8, CD56, CD14, CD38, IgK, IgL, TRBC1, TRBC2, TCRgamma/delta, TCRalpha/beta. FCM showed 94 % of T-cells of Tfh phenotype, CD4+, with normal distribution of TRBC1/2. There were 3 % of B-cells with polyclonal phenotype.

Cytogenetics

not performed

Molecular Studies

EuroClonality-NDC assay on AvitiLT – no mutations of rearrangement found

Proposed Diagnosis

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), with T-cell/histiocyte-rich large B-cell lymphoma-like/THRLBCL-like pattern E (90%) and T-cell rich nodular pattern D (10%)

Interesting Feature(s)

Predominance of diffuse THRLBCL-like pattern may cause diagnostic challenge when differentiating NLPHL from DLBCL/LBCL. Adequate sampling and search for other NLPHL patterns may help to establish proper diagnosis. In this case also the age of the patient was a clue favouring the diagnosis of NLPHL. However, seemingly negative results of flow cytometry and unhelpful “silent” results of NGS could have posed as potential diagnostic pitfall.

Panel Diagnosis: NLPB/HL, pattern E

EA4HP26-LYWS-134

Relapsing T-cell histiocyte rich B-cell lymphoproliferation – NLPHL pattern E or THRLBCL?

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Case Description

Sixty-five-year-old female presented with enlarged axillary lymph nodes 12/24. Lymphoma with diffuse growth, rich T-cell/histiocyte background and atypical B-cells (more than 10%) was seen. Rearrangements in IgH and IgKappa were found. Diagnosis was established as nodular lymphocyte-predominant Hodgkin lymphoma with growth pattern E. Staging revealed generalized lymphadenopathy, splenomegaly and involvement of bone marrow. Patient underwent treatment with R-CHOP (5 cycles) with early relaps in 8/25 with cervical lymphadenopathy and similar infiltration with diffuse lymphoma with slight change of phenotype. Infiltration of bone marrow was proved again.

Biopsy Fixation Details

buffered formalin

Frozen Tissue Available

NO

Details of Microscopic Findings

Primary biopsy (LN1): Enlarged lymph node with small areas of residual nodules of B-cells with scattered larger atypical cells (resembling LP cells) and with predominantly diffuse growth of small lymphocytes and histiocytes and dispersed larger atypical neoplastic cells (exceeding 10% of the cellularity). Involvement of bone marrow (BM1).

Relapse biopsy (LN2): Two small lymph nodes (up to 10 mm) with diffuse infiltration with same diffuse lymphoma, with increased proportion of CD30+ cells. Bone marrow (BM2) infiltrated (40%) by with reduced expression of CD20 in neoplastic cells.

Immunophenotype

Neoplastic cells: CD20, PAX5, BOB1-positive, with Ki67 at 50%. Bcl6 and EMA in minority of cells. Individual cells expressing CD30 (negative for CD15 and EBER). Reduced expression of CD20 at relapse with higher proportion of larger CD30+ dim PAX5 cells with retained CD20, BOB1 and LCA.

Phenotype of the background: CD3+ T-cells with similar proportion of CD4+ and CD8+ cells. PD1+ in most of the T-cells, CD57 and TIA in 20-30% of T-cells. Follicular dendritic cells (CD21, CD23) mostly negative in diffuse area. Prominent population was composed of histiocytes positive for CD68 and CD163.

Flow cytometry (bone marrow aspirate): performed from BM2 – population of 3.7 % of lymphoplasmacytic cells with CD45, CD19, CD27, dim CD79a, dim CD38 and CD138, with slight predominance of kappa light chain expression was seen, without expression of CD20.

Cytogenetics

not performed

Molecular Studies

1) Clonality testing with PCR (EuroClonality/BIOMED-2): BCR – IgH FR1/2 clonal peaks, IgKappa-Vk-Kde, intron Kde – suspicious clonal peaks; TCRB/C/D polyclonal.

2) NGS with EuroClonality-NDC assay on AvitiLT – mutation of *TNFAIP3*, *DNMT3A* and *NOTCH1*. IGK: IGKV2-28, Kde was unproductive, no IgH rearrangement.

Proposed Diagnosis

T-cell histiocyte rich B-cell lymphoproliferation – NLPHL pattern E or THRLBCL with increased number of neoplastic cells

Interesting Feature(s)

T-cell/histiocyte-rich B-cell lymphoproliferation – original diagnosis preferred NLPHL with pattern E growth however certain overlap with THRLBCL is seen but the number of atypical / neoplastic cells exceeds 10% of the infiltrate. Also, significant proportion of cells, especially in relapsed material, shows CD30 positivity.

Panel Diagnosis: NLPB/HL, pattern E

EA4HP26-LYWS-135

Case of phenotypic overlap between nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma

PhD/MD Katerina Kamaradova^{1,2}

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Case Description

Fifty-six-year-old male presented with enlarged inguinal lymph nodes. Specimen included larger node 2,3 cm in diameter and small lymph node 0,7 mm in diameter. Case was sent to our department for second opinion, no further follow up is available at this point.

Biopsy Fixation Details

buffered formalin

Frozen Tissue Available

NO

Details of Microscopic Findings

Enlarged lymph node with effaced architecture and different growth areas. At the periphery the lymph node had vaguely nodular structure with predominance of small lymphocytes and dispersed larger atypical cells with multilobated nuclei (LP cells) surrounded with small lymphocytic rosettes. Other part of the lymph node showed diffuse areas with proliferation of histiocytes, small to medium sized lymphocytes and larger neoplastic cells. The atypical neoplastic cells were occasionally having H/RS-like morphology.

Immunophenotype

Neoplastic cells with LP morphology were positive for CD20, PAX5, bcl6 and dim MUM1. They were negative for GATA3. In part of the lymph node, the atypical cells showed CD30 positivity, dim PAX5 and CD15 expression, as well as focal positivity for EBER.

Phenotype of the background showed predominance of CD4+ T-cells in both areas. T-cells were partially positive for CD57, PD1 and GATA3 and were forming rosettes around LP cells. Follicular dendritic cells (FDC, CD21) were mostly destroyed and in more diffuse areas were vanished. Expression of CD8 was seen in about 30 % of T-cells in the background. Overall proliferation in Ki67 was about 25%.

Cytogenetics

not performed

Molecular Studies

not performed

Proposed Diagnosis

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), pattern D and E with phenotypic overlap with classical Hodgkin lymphoma.

Interesting Feature(s)

Phenotypically, the case shows features consistent with the NLPHL diagnosis (LP cells, T-cell rosettes), however, part of the atypical cells have Hodgkin-like morphology and classical Hodgkin phenotype including EBER positivity. Nevertheless, rare cases of EBV-positive NLPHL exist as well keeping the classification dilemma broader.

Panel Diagnosis: NLPB/HL, pattern E, w/ EBV+ cells

EA4HP26-LYWS-136

Epstein-Barr virus positive diffuse large B-cell lymphoma

Dr. Maria Y. Chen, Dr. Robert P. Hasserjian

Massachusetts General Hospital, Pathology, Boston, USA

Case Description

A 70-year-old man with a history of Crohn's disease and IBD-related arthritis presents for evaluation of urinary frequency, dysuria, and hematuria. He also has a history of EBV+ diffuse large B-cell lymphoma (EBV+DLBCL), for which he received R-CHOP and was in complete remission as of his last hematology-oncology visit 8 years ago. A CT was performed and found new multifocal PET-avid lymphadenopathy. A biopsy showed recurrent EBV+DLBCL.

Biopsy Fixation Details

Tissue was fixed with formalin and paraffin embedded.

Frozen Tissue Available

Yes.

Details of Microscopic Findings

The core biopsies from the enlarged left neck lymph node showed a diffuse infiltrate of scattered and loosely clustered large, pleomorphic atypical lymphoid cells with an abundant background of small lymphocytes and histiocytes. There are areas with significant sclerosis and patchy geographic necrosis.

Immunophenotype

By immunohistochemistry, the large atypical cells are positive for CD20, CD79a, PAX5 (large subset), MUM1, CD30 (moderate staining in 30%), and EBV LMP1 and negative for EBV EBNA2; CD15 stains few scattered large cells. In-situ hybridization for Epstein-Barr virus encoded RNA (EBER) is positive in the large cells. CD3 highlights scattered small T cells.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

Epstein-Barr virus positive diffuse large B cell lymphoma, not otherwise specified.

By morphology, this is favored to represent recurrent disease. However, a new primary cannot be completely excluded.

Interesting Feature(s)

- Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL) is defined as a monoclonal large B-cell lymphoma in which EBV is present in the majority of large B cells in the absence of an immunodeficiency or lymphoma (Anagnostopoulos et al, 2024)
 - Prevalence varies by region, but is low in Western countries and higher in Asia, Africa, and Latin America (4% to 28% of DLBCL).
 - Most occur in older patients (≥50 years old), but can occur in younger individuals (Nicolae et al, 2015).
 - Historically have had worse prognosis than EBV- DLBCL, but may be changing in era of new therapies (Malpica et al, 2024).
- Histologically divided into polymorphic versus monomorphic types (Malpica et al, 2024).
 - Polymorphic: more common, with scattered large cells in a background of numerous small lymphocytes or histiocytes, resembling T-cell/histiocytes rich large B-cell lymphoma.
 - Monomorphic: consists of sheets of atypical large cells, resembling DLBCL.
 - Angiocentric lesions and extensive geographical necrosis are common findings.
- Most cases have an activated/nongerminal center B-cell immunophenotype and have EBV latency type II, with LMP1 having been shown to mediate PDL1 overexpression (Chen et al, 2013).
- Late recurrence (>24 months) is rare; few studies with limited sample size suggest that patients with relapsed/refractory EBV+DLBCL may benefit from treatment with PD-1 inhibitors and EBV-targeted therapies (Haverkos et al, 2023; Li et al, 2024).
- The gain of CD30 in a subset of cells and rare CD15 positivity in the recurrent lymphoma is of unknown significance.

Panel Diagnosis: EBV+ DLBCL

When Metastatic Carcinoma Is Not the Answer: EBV-Positive Diffuse Large B-Cell Lymphoma With Granulomatous Features in the Liver

Dr. Rakshit Tyagi¹, Dr. Jonathan Said¹, Dr. Steven Tsai², Dr. Christian Hirt¹

¹ David Geffen School of Medicine at UCLA, Department of Pathology & Laboratory Medicine, Los Angeles, USA; ² David Geffen School of Medicine at UCLA, Department of Hematology/Oncology, Los Angeles, USA

Case Description

A 75-year-old male with a history of polycythemia vera, prostate cancer, and high-grade papillary urothelial carcinoma of the bladder presented to the emergency department with lethargy and weakness. Complete blood count revealed pancytopenia. Positron emission tomography demonstrated widespread FDG-avid lymphadenopathy and multiple splenic, hepatic, and osseous lesions, raising concern for metastatic cancer.

Biopsy Fixation Details

Liver lesions were targeted for CT and ultrasound-guided biopsy. Soft tissue biopsy cores were placed in formalin fixative for further processing.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Histologic sections of the tissue cores demonstrate liver parenchyma with vaguely granulomatous areas comprised of an abundant lymphohistiocytic infiltrate. Scattered large malignant cells are present, characterized by irregular nuclear contours, multinucleation, prominent nucleoli, and abundant eosinophilic cytoplasm. In addition, there are frequent Hodgkin/Reed/Sternberg-like cells giving a Hodgkin-like appearance. Occasional mitotic figures and apoptotic bodies are identified. Focal areas show coagulative geographic necrosis. The uninvolved liver parenchyma demonstrates increased large-droplet macrovesicular steatosis (approximately 20%) and dilated sinusoids.

Immunophenotype

Immunohistochemistry highlights scattered malignant cells that are positive for CD19, PAX5, CD30, CD45 (partial), BCL6, MUM1, PD-L1, Kappa ISH, c-MYC, and EBV-EBER ISH with an estimated Ki-67 proliferation index of approximately 90%. The malignant cells are negative for CD5, CD10, CD20, CD15, BCL1, BCL2, and ALK.

Cytogenetics

Fluorescence in situ hybridization (FISH) studies performed using *BCL6* and *MYC* break-apart probes, as well as *MYC-IGH* and *IGH-BCL2* dual fusion probes, demonstrated normal signal patterns.

Molecular Studies

Next-generation sequencing performed on formalin-fixed, paraffin-embedded (FFPE) biopsy tissue identified pathogenic mutations in *JAK2* p.V617F (variant allele frequency [VAF] of 31.2%) and *SF3B1* p.K666N (VAF 16.5%). A variant of uncertain significance (VUS) was also identified in *PTPN11* p.T153A (VAF 39.7%).

Proposed Diagnosis

EBV-positive diffuse large B-cell lymphoma

Interesting Feature(s)

The clinical and imaging presentation in this case initially favored metastatic carcinoma due to widespread FDG-avid lesions. Histologic evaluation initially favored a preliminary diagnosis of a T-cell/histiocyte-rich large B-cell lymphoma. However, with positive EBV-encoded RNA in situ hybridization (EBER ISH), the diagnosis was revised to EBV-positive diffuse large B-cell lymphoma (EBV+ DLBCL). EBV+ DLBCL is characterized by morphologic heterogeneity, including polymorphic and monomorphic patterns with abundant reactive components and Reed-Sternberg-like cells, leading to potential confusion with other lymphoma subtypes and carcinoma, particularly on small biopsies. EBER ISH is essential for distinguishing these cases and avoiding misclassification.

Panel Diagnosis: EBV+ DLBCL

B-Cell Lymphoma with Reed–Sternberg–Like Cells and a Prominent Histiocytic Background: A Diagnostic Challenge

Dr. Mona Sharief, Dr. Hariharan Bharadwaj

UMass Chan Medical School, Baystate Medical Center, Springfield, USA

Case Description

An 84-year-old male with a medical history of hypertension, diabetes mellitus, and hypothyroidism presented to the emergency department with recurrent falls, fatigue, and weight loss. Radiographic imaging revealed multiple bilateral pulmonary nodules; mediastinal, right hilar, gastro-hepatic, and retroperitoneal lymphadenopathy. Additional nodules in the liver, spleen, and right adrenal gland raised concern for metastases. Histopathological examination of a lung nodule confirmed pulmonary adenocarcinoma, with a concurrent biopsy of a retroperitoneal lymph node performed for further evaluation.

Biopsy Fixation Details

Two core biopsies of soft, tan-red tissue measuring 1.4 x 0.1 cm and 1.7 x 0.1 x 0.1 x 0.1 were obtained and preserved in 10% neutral buffered formalin. The specimens were processed entirely for histologic evaluation.

Frozen Tissue Available

No frozen tissue was submitted.

Details of Microscopic Findings

Histologic analysis of the lymph node revealed complete effacement of nodal architecture by sheets of histiocytes and mixed inflammation including small lymphocytes and scattered eosinophils. Within this background, rare, highly atypical large cells were identified exhibiting vesicular chromatin, prominent 'cherry-red' nucleoli, and moderate-to-abundant clear-to-eosinophilic cytoplasm. A subset of these cells was binucleate, consistent with Reed-Sternberg (RS) or RS-like morphology. Additional findings included scattered mummified cells.

Immunophenotype

Immunohistochemical staining demonstrated that the large, atypical cells were positive for CD20, CD79a, CD30, and MUM1, with strong PAX5 in a subset (overall heterogeneous). The cells were negative for CD15, ALK1, STAT6, GATA3, and keratin cocktail. EBV-encoded RNA in-situ hybridization (EBER-ISH) was negative. PGM1 highlighted the histiocytes, while CD45 identified background histiocytes and lymphocytes, though expression in the larger atypical cells was difficult to evaluate. Additionally, CD3 and CD20 highlighted background T-cells and scattered small B-cells, respectively.

Cytogenetics

Not performed

Molecular Studies

Not performed in the lymph node biopsy

Proposed Diagnosis

Large cell lymphoma with Reed-Sternberg cell morphology and B-cell immunophenotype

Interesting Feature(s)

The differential diagnosis considered in our case included Diffuse Large B-cell Lymphoma, Not Otherwise Specified (DLBCL-NOS), classic Hodgkin lymphoma (cHL), and the rare primary “extramediastinal” grey zone lymphoma (PEMGZL). While the presence of large, atypical cells, strong B-cell immunophenotypic expression, and architectural effacement aligns with DLBCL, the prominent histiocytic and T-cell-rich background is atypical for standard presentation. Conversely, although the reactive microenvironment containing CD30+ RS cells suggests cHL, the diagnosis is confounded by the strong expression of B-cell markers CD20 and CD79a, alongside the absence of CD15, STAT6, and GATA3. PEMGZL was also considered; however, in accordance with WHO recommendation,

cases presenting with overlapping features outside the mediastinum are preferentially classified as DLBCL-NOS. This case illustrates the challenging diagnostic spectrum of B-cell malignancies in which architectural and immunophenotypic features do not align with a single classic entity. Specifically, the presence of RS-like cells along with the microenvironment creates significant diagnostic overlaps between cHL and B-cell non-Hodgkin lymphomas. Distinguishing between these entities is vital, as accurate classification is paramount for determining appropriate clinical management and predicting patient prognosis.

Panel Diagnosis: Large cell lymphoma with Reed-Sternberg cell morphology and B-cell immunophenotype

EA4HP26-LYWS-145

Histiocyte-rich Germinal Center-Type Diffuse Large B-cell Lymphoma Arising in the Setting of Common Variable Immunodeficiency

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Case Description

52-year-old man with common variable immunodeficiency (CVID) on weekly subcutaneous immunoglobulin replacement and immune thrombocytopenia on avatrombopag presented with diffuse lymphadenopathy and enlarging pulmonary masses. An initial core biopsy of a level 11 lymph node (LN) demonstrated a diffuse histiocytic infiltrate with scattered and focally aggregated large atypical B cells. These B-cell aggregates appeared to be associated with CD21-positive follicular dendritic cell (FDC) meshworks, and given the paucity of the diagnostic lesional tissue and the obscuring histiocytic background, definitive classification could not be made. Due to persistent clinical concern, an excisional biopsy of the level 7 LN was performed, which confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL), germinal center (GC) subtype in the setting of CVID.

Biopsy Fixation Details

Formalin-fixed (10%)

Frozen Tissue Available

No

Details of Microscopic Findings

Initial core biopsy showed limited lymphoid tissue with architectural effacement by numerous histiocytes and scattered small to large lymphocytes. Larger cells showed irregular nuclear contours, condensed chromatin, inconspicuous nucleoli, and scant cytoplasm. The lesional process was partly obscured by numerous histiocytes, with only a small focus of denser lymphoid proliferation. The limited tissue constrained evaluation; therefore, an excisional biopsy was performed, which confirmed DLBCL, GC-subtype.

Immunophenotype

The large B cells expressed CD20, PAX5, CD10 (weak), BCL2 (variable), BCL6, and MUM1, and were negative for CD23, CD30, MYC, and cyclin D1. Admixed were many CD68-positive histiocytes. CD21 and CD23 showed focal FDC meshwork staining. The ki-67 proliferation index was high (80%). EBER in situ hybridization was negative. AFB and GMS were negative for microorganisms.

Cytogenetics

FISH on both biopsies was negative for IGH::BCL2 and IGH::MYC fusions and for BCL6 rearrangement (200 nuclei each: CEP8/MYC/IGH, IGH/BCL2, BCL6). Karyotype and molecular data are not available.

Molecular Studies

Not performed

Proposed Diagnosis

DLBCL, GC-subtype, arising in CVID

Interesting Feature(s)

We describe a unique case of a histiocyte-rich GC-subtype DLBCL arising in a patient with CVID. While CVID is a well-established risk factor for B-cell lymphomas and granulomatous disease, likely driven by chronic antigenic stimulation, impaired immune surveillance, and dysregulated GC reaction, those with a histiocyte-rich background in this context has not been systematically characterized. In this case, the striking abundance of histiocytes partially obscured the neoplastic B-cell population, illustrating the paradoxical coexistence of impaired humoral immunity with immune hyperactivation. This finding raises questions about altered macrophage recruitment in CVID-associated lymphomagenesis. Clinically, CVID patients who develop lymphoma often exhibit antecedent immune abnormalities, including chronic lymphadenopathy, splenomegaly, and autoimmune cytopenias. These features can blur the distinction between benign immune dysregulation and overt malignancy, complicating timely diagnosis. This case underscores the need for heightened diagnostic vigilance in CVID patients with progressive lymphadenopathy and illustrates the complex interplay between immune dysregulation and lymphoid neoplasia.

Panel Diagnosis: DLBCL, GC-subtype, arising in CVID

EA4HP26-LYWS-146

Splenic marginal zone lymphoma with extensive sarcoid-like granulomatous inflammation

Dr. Luke Bushrow, Dr. Arwa Shana'ah, PhD/MD Yulan Jin

Ohio State University, Pathology, Columbus, USA

Case Description

A 64-year-old man with a recent history of cholecystectomy presented with fever and edema. Workup revealed marked splenomegaly (23 cm), thrombocytopenia (58 K/ μ L), anemia (hemoglobin 9.3 g/dL), elevated serum angiotensin-converting enzyme (ACE) levels (245 U/mL), and hypercalcemia (11.4 mg/dl).

Bone marrow biopsy showed 10-20% involvement by a CD5-negative CD10-negative kappa-restricted B-cell population. Subsequent splenectomy revealed findings consistent with splenic marginal zone lymphoma with extensive background non-necrotizing granulomatous inflammation. Outside pathology review of a liver biopsy obtained at the time of cholecystectomy reported poorly formed granulomas, lymphocytic inflammation involving portal tracts, and Batts–Ludwig stage 1 fibrosis.

Following splenectomy, the patient's symptoms resolved. Based on extensive laboratory and radiologic evaluation and the absence of stereotypical sarcoidosis sequelae (pulmonary, cutaneous, mediastinal, ocular, joint, or neurological involvement) the patient was determined not to have sarcoidosis by rheumatology and pulmonology consultants. The patient subsequently received rituximab therapy for 4 months and has remained without clinical or radiologic evidence of persistent or recurrent disease at last follow-up (18 months post-splenectomy).

Biopsy Fixation Details

Spleen tissue was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections show splenic parenchyma with replacement of the white pulp by atypical nodular lymphoid proliferation composed of monotonous, medium-sized lymphoid cells with round to angulated nuclear contours and inconspicuous nucleoli. Numerous non-necrotizing granulomas, including multinucleated giant cells, are seen at the

periphery of and within the nodular lymphoid aggregates. Granulomas are also identified in the red pulp. The splenic hilar lymph nodes show similar histologic findings.

Immunophenotype

By flow cytometry:

- Positive: CD19, CD20, CD27, surface kappa light chain
- Negative: CD5, CD10, CD23, CD123, CD103, CD25, CD11c, surface lambda light chain

By immunohistochemistry:

- Positive: CD19, CD20, PAX5, BCL2, Ki-67 (<10%)
- Negative: CD5, CD10, CD30, CD43, BCL1, BCL6, c-MYC, MUM1, TdT

Other stains:

- Negative for EBER ISH
- AFB, GMS, and PAS stains negative for microorganisms

Cytogenetics

Complex karyotype with multiple structural/numerical abnormalities including monosomy 17 resulting in loss of TP53.

Molecular Studies

Next generation sequencing panel detected no pathogenic somatic variants.

Proposed Diagnosis

Splenic marginal zone lymphoma

Interesting Feature(s)

Although granulomatous reactions are fairly common in both Hodgkin lymphoma and T-cell lymphoma, they are relatively rare in non-Hodgkin B-cell lymphomas, and the mechanism underlying this phenomenon remains unknown. The presence of prominent non-necrotizing granulomatous inflammation in the spleen, elevated serum ACE levels and hypercalcemia, makes the diagnosis challenging and may result in misdiagnosis as sarcoidosis if the underlying lymphoma is overlooked.

The complex karyotype and TP53 deletion identified in this case are recurrent cytogenetic abnormalities commonly associated with poor prognosis in many malignancies, including splenic marginal zone lymphoma. In contrast, lymphoma patients with granulomatous reactions have been reported to demonstrate better treatment responses and prognosis. It would therefore be of interest to investigate the interplay between these two prognostic factors in disease progression.

Panel Diagnosis: PICTURES NOT SENT; NOT DISCUSSED

EA4HP26-LYWS-151

Nodular lymphocyte -predominant Hodgkin lymphoma/ nodular lymphocyte predominant B-cell lymphoma (NLPHL/NLPBL) pattern E with an aggressive clinical course and complications of hemophagocytic lymphohistiocytosis (HLH)

Dr. Sahil Chaudhary, Dr. Ifeyinwa E. Obiorah

University of Virginia Health, Charlottesville, USA

Case Description

The patient was a 27-year-old man who initially presented with a palpable lump in the left axilla. Ultrasound imaging demonstrated multiple pathologically enlarged lymph nodes measuring up to 5 cm. A CT scan of the chest performed approximately one month later revealed bulky left subpectoral and axillary lymphadenopathy, additional smaller mediastinal lymph nodes, partially visualized upper abdominal adenopathy, and suspected splenic lesions.

Laboratory evaluation showed elevated liver function tests. An excisional biopsy of the left axillary lymph node was performed. The patient was treated sequentially with multiple cycles of chemotherapy, resulting in initial disease regression. However, five months later, follow-up CT imaging demonstrated disease progression, with biopsy confirming residual disease. Despite aggressive therapy, the disease progressed to involve the bone marrow and was complicated by hemophagocytic lymphohistiocytosis (HLH). The patient died shortly thereafter, approximately one year after the initial diagnosis

Biopsy Fixation Details

The lymph node was fixed in formalin, and the bone marrow biopsy was fixed in Formalin then decalcified in formic acid.

Frozen Tissue Available

No

Details of Microscopic Findings

The lymph node architecture was largely effaced by a predominantly diffuse atypical lymphoid infiltrate composed of medium- to large-sized atypical lymphoid cells with irregular nuclear contours, vesicular chromatin, inconspicuous nucleoli, and frequent multilobated forms. Focal areas showed a nodular growth pattern with small lymphoid cells and histiocytes admixed with scattered large cells consistent with LP cells. Both the diffuse and nodular areas contained abundant small lymphocytes and numerous histiocytes. The bone marrow was infiltrated with the same large atypical lymphoid cells in a background of small lymphocytes and numerous histiocytes with hemophagocytosis.

Immunophenotype

The large atypical cells are positive for CD20, OCT2, CD79a, PAX5, and BCL6 and negative for IgD, CD15 and ALK1. CD30 is focally stains some larger cells with immunoblastic morphology. CD3 stains numerous background T cells which are positive for PD1. CD21 and CD23 reveal few disrupted follicular dendritic cell meshwork. EBV-ISH RNA stain is negative.

Cytogenetics

FISH studies were negative for MYC, BCL2 and BCL6 gene rearrangements.

Molecular Studies

None

Proposed Diagnosis

T cell/histiocyte rich large B cell lymphoma transformed from Nodular lymphocyte -predominant Hodgkin lymphoma/nodular lymphocyte predominant B-cell lymphoma (NLPHL/NLPBL) pattern E.

Interesting Feature(s)

The patient was a young adult male who presented with rapidly progressive, and extensive lymphadenopathies with early extranodal involvement, which is atypical for classic indolent NLPHL.

Histologically, the Pattern E variant, characterized by a diffuse T-cell-rich background with scattered LP ("popcorn") cells, with T-cell/histiocyte-rich large B-cell lymphoma (THLBCL)-like areas, posing a significant diagnostic challenge.

Clinically, the disease followed an unexpectedly aggressive course, with early treatment resistance, rapid relapse after initial therapy, and progression to bone marrow involvement to THLBCL complicated by hemophagocytic lymphohistiocytosis (HLH), a rare and life-threatening association.

The combination of advanced-stage disease, bulky adenopathy, poor response to standard therapies, and development of HLH underscores the biological heterogeneity of NLPHL and highlights Pattern E as a high-risk variant that may behave more like an aggressive B-cell lymphoma than a classic NLPHL subtype.

Panel Diagnosis: NLPB/HL, pattern E (THRLBCL-like), clinical progression with HLH

Follicular lymphoma with prominent histiocytic expansion

Dr. Nathanael Bailey, Dr. Joanna Dalland, Dr. Rebecca King, Dr. Karen Rech

Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, USA

Case Description

80-year-old male with reported history of relapsed diffuse large B-cell lymphoma treated with transplant 10 years prior to this biopsy. Now presenting with diffuse PET-avid lymphadenopathy. A left axillary lymph node biopsy was performed.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The nodal architecture is effaced by a diffuse lymphohistiocytic proliferation. The lymphocytes are predominantly small, and scattered, with some occasional larger forms and forms with plasmacytoid morphology. No follicular architecture is present. There are abundant histiocytes throughout the paracortex, some of which exhibit nucleoli and some with possible emperipolesis. No histiocytic proliferation within sinusoids is seen.

Immunophenotype

The neoplastic B-cells express pan-B-cell antigens, CD10, BCL6, MEF2B, BCL2, and kappa immunoglobulin. CD21 stains only rare follicular dendritic networks. EBV is negative. The histiocytes are partially positive for S100 and express cyclin D1. OCT2 appears to be weakly positive in a subset. The histiocytes are negative for CD1a, langerin, BRAF V600E, and ALK. GMS and AFB stains are negative.

Cytogenetics

FISH studies document the presence of *BCL2* rearrangement. No rearrangements of *MYC* or *BCL6* are identified.

Molecular Studies

Not performed

Proposed Diagnosis

Follicular lymphoma with prominent reactive histiocytic expansion

Interesting Feature(s)

The degree of histiocytic proliferation in the lymph node is such that the lymphoma was somewhat masked histologically. Due to the presence of some S100 positivity in histiocytes, the case was referred to us with concern for Rosai Dorfman Destombes disease. However, the paracortical nature of the proliferation and lack of sinusoidal involvement, along with the other histologic features militate against the diagnosis. The follicular lymphoma itself is unusual in that it lacks follicular architecture and exhibits some morphologic plasmacytoid differentiation. However, the germinal center immunophenotype and *BCL2* rearrangement support the classification.

Panel Diagnosis: FL w/ Rosai Dorfman areas

NLPHL/NLPBL and DLBCL: Composite or transformation?

Dr. Rodrigo D.A. Natal, Dr. Humberto C. Carneiro, Dr. Marianne D.C. Gonçalves

Hospital São Luiz – Rede D'Or, Anatomic Pathology D'Or Hospital Network, São Paulo, Brazil

Case Description

A 33-year-old previously healthy man presented with marked enlargement of left axillary lymph nodes over the past 45 days. He reported only two febrile episodes, with no other associated symptoms. Imaging studies, including ultrasound and PET-CT, demonstrated isolated left axillary lymphadenopathy, with the largest lymph node measuring 9.0 cm. All other laboratory tests were within normal limits.

After treatment with chemotherapy, there has been no evidence of disease persistence or recurrence to date, with a 6-month follow-up.

Biopsy Fixation Details

An excisional biopsy of the left axillary lymph node was performed and fixed in 4% buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Histological sections revealed a lymph node with altered architecture due to the presence of three distinct components.

The first component showed a proliferation of large lymphoid cells with monolobated nuclei, granular chromatin, visible nucleoli, and moderate amphophilic cytoplasm, occasionally forming large nodular architectural patterns. There was a relative paucity of small lymphocytes, histiocytes, eosinophils, and plasma cells.

The second component consisted of a proliferation of lymphoid cells with enlarged, lobulated nuclei, dense chromatin, prominent nucleoli, and abundant amphophilic cytoplasm. Numerous small lymphocytes without atypia were interspersed among the enlarged cells, sometimes forming a nodular architectural pattern.

The third component demonstrated a proliferation of lymphoid cells with enlarged, lobulated nuclei, dense chromatin, inconspicuous nucleoli, and abundant amphophilic cytoplasm. Numerous small lymphocytes without atypia and histiocytes were interspersed among the enlarged cells, showing a diffuse architectural pattern.

Immunophenotype

The immunophenotype of the first component showed neoplastic cells positive for CD45, CD79a, CD20, PAX5, BOB.1, OCT2, CD10, BCL6, and CD23, with partial expression of CD30, MUM1, fascin, c-MYC, and BCL2. The neoplastic cells were negative for CD15, EMA, ALK, and GATA3.

In the second component, neoplastic cells were positive for CD45, CD79a, CD20, PAX5, BOB.1, OCT2, and BCL6, with partial expression of CD30, MUM1, c-MYC, BCL2, and CD23. They were negative for CD15, EMA, CD10, fascin, ALK, and GATA3.

The third component showed neoplastic cells positive for CD45, CD79a, CD20, PAX5, BOB.1, OCT2, and BCL6, with partial expression of CD30, MUM1, c-MYC, BCL2, and CD23. The cells were negative for CD15, EMA, fascin, CD10, ALK, and GATA3.

Cytogenetics

Not available.

Molecular Studies

Not available.

Proposed Diagnosis

Nodular lymphocyte-predominant Hodgkin lymphoma / nodular lymphocyte-predominant B-cell lymphoma (NLPHL/NLPBL), patterns C and E, associated with diffuse large B-cell lymphoma (DLBCL), germinal center B-cell type (GCB).

Interesting Feature(s)

This case illustrates a rare presentation of NLPBL/NLPBL with concurrent DLBCL in a young adult male, presenting as isolated bulky axillary lymphadenopathy with minimal systemic symptoms. Histologic evaluation of a single lymph node revealed coexisting NLPBL patterns C and E, and a DLBCL component, supporting a morphologic continuum from indolent disease to aggressive transformation and reinforcing the biologic relationship between these entities as recognized in current WHO/ICC classifications.

Panel Diagnosis: NLPB/HL, multiple patterns

EA4HP26-LYWS-174

Rapidly Progressive "Sarcoidosis"

Dr. Claudio Mosse

Vanderbilt University Medical Center, Pathology, Microbiology, and Immunology, Nashville, USA

Case Description

The patient is a 72-year-old woman who presented with left cervical adenopathy that on biopsy at the outside hospital showed noncaseating granulomas consistent with sarcoidosis. Her cervical lymphadenopathy continued to worsen for 6 months before she started on prednisone. After initiating prednisone, the lymphadenopathy waxed and waned for the next 9 months with new lymphadenopathy in left axilla, mediastinum, upper abdominal, and splenomegaly. Although other FNAs and core biopsies had shown granulomas consistent with sarcoidosis, the marked asymmetry of involvement, worsening B symptoms, and growth on high dose steroids led to a consideration of lymphoma. After 23 months of therapy for sarcoidosis, she underwent laparoscopy to obtain a larger piece of tissue from multiple PET avid sites including omentum, liver, and falciform ligament.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

None

Details of Microscopic Findings

There is an extensive lymphohistiocytic infiltrate with noncaseating granulomas, small lymphocytes, and rare, large atypical lymphocytes with convoluted nuclei, vesicular chromatin, prominent nucleoli, and moderate clear cytoplasm.

Immunophenotype

The large atypical cells are positive for CD20, CD79a (weak), CD30 (focal weak), and PAX5 (weak) and are negative for CD15 and EBER. Histiocytes are strongly positive for CD163, while most of the background, small lymphocytes are CD3+ T cells. There is no significant population of CD138+ plasma cells or of IgG4+ cells. GMS and Ziehl-Neelsen AFB special stains are negative for microorganisms.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

T-cell/ Histiocyte-rich Large B Cell Lymphoma.

Interesting Feature(s)

This case presents several interesting features. First, the patient presented with unilateral cervical lymphadenopathy and received a fine needle aspirate (FNA) and core biopsy showing noncaseating granulomas consistent with sarcoidosis. While there is a reported association between sarcoidosis and lymphoma, this case exemplifies that

lymphomas associated with dense reactive infiltrates and few tumor cells may potentially be misdiagnosed on small biopsies. In fact, after 6 cycles of Pola-R-CHP, the patient developed a new lung mass and underwent transbronchial cryobiopsy. Multiple levels through the tissue with multiple rounds of IHC showed granulomatous inflammation with no large B cells detected. The clinical team determined that this likely represented a sarcoidosis flair after ending chemotherapy rather than relapse although the inflammation was very similar to that seen in the lymphoma biopsy. The overlap between sarcoidosis and lymphoma may require multi-disciplinary approach to distinguish.

Second, the case was a challenging diagnosis as many pieces of biopsied tissue only showed granulomatous inflammation with no large lymphocytes. Multiple prior biopsies had failed to detect lymphoma, and sufficient material was obtained only because the patient's clinical condition was rapidly worsening, discordant with typical clinical course of sarcoidosis. Challenging diagnoses may require sufficient tissue sampling.

Third, many areas of the biopsies were involved by granulomatous inflammation but only a few areas showed large abnormal B cells. Some B cell markers were weak – possibly due to prior sarcoidosis therapy with corticosteroids – including weak CD79a and variable CD20. Therapy for benign diagnoses may complicate the diagnosis of lymphoma.

Panel Diagnosis: De novo THRLBCL

EA4HP26-LYWS-187

28-year-old female with 6.3-cm enlarged axillary lymph node

Dr. Fnu Monika, Dr. Ling Zhang

Moffitt Cancer Center, Hematopathology, Tampa, USA

Case Description

28-year-old female presented with a lump in her right axilla around 5 months ago. She denied night sweats, fatigue, or any significant medical history. Laboratory studies revealed normal CBCs and LDH levels, and negative serologies for HIV, HCV, and HBV. Subsequent CT scan showed right axillary lymphadenopathy measuring up to 6.3 x 4.9 cm. An excisional biopsy was performed at outside hospital, and the slides were requested for review at our institution. Bone marrow staging was negative for lymphoma involvement.

Biopsy Fixation Details

10% formalin fixation

Frozen Tissue Available

NA

Details of Microscopic Findings

Review of H&E sections showed lymph node architecture was completely effaced with scattered large, atypical lymphoid cells morphologically resembling lymphocyte predominant (LP) cells embedded in the background of diffuse proliferation of small lymphocytes mixed with histiocytes and focal necrosis. The LP cells were large with occasional multilobulated nuclei and prominent eosinophilic nucleoli, distributed singly and in small clusters. Several residual follicles were present in the periphery.

Immunophenotype

All submitted immunohistochemical stains with appropriate controls were reviewed. The large, atypical cells (LP) were positive for CD45, CD20, CD79 (strong), OCT2, BOB1, PAX5, CD15 (strong), BCL6, and MUM1 (dim) and were negative for CD30, CD5 and CD10. Several small mature B-cell nodules present in the periphery were stained positive for CD20, CD79, and PAX5. CD3 and CD5 highlighted diffuse T-cell proliferation in the background with rosette formations around LP cells. PD-1 highlighted rosettes in peripheral nodules but was negative in diffuse T-cell/histiocyte rich areas, while CD21 showed absence of follicular dendritic meshworks in diffuse areas with preservation in peripheral follicles. The Ki-67 was increased in LP cells. EBER-ISH was negative. AFB and GMS

were negative for microorganisms.

Corresponding flow cytometry showed no monoclonal B-cell or an aberrant T-cell population.

Cytogenetics

NA

Molecular Studies

NA

Proposed Diagnosis

Nodular lymphocyte predominant B-cell lymphoma, pattern E (ICC 2022)

Nodular lymphocyte predominant Hodgkin lymphoma, pattern E (5th Ed WHO)

Interesting Feature(s)

This represents a diagnostically challenging case with clinical, morphologic and immunophenotypic overlap between nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), pattern E, and T-cell/histiocyte rich B-cell lymphoma (THRBCL). Tumor cells are associated with focal necrosis, increased Ki67 proliferation rate, diminished dendritic meshworks and strong CD15 expression, which are unusual features for NLPHL but have been previously reported. Prior studies have shown that certain variants of NLPHL, particularly pattern D and E, are more associated with advanced stage and have a higher risk of relapses in the first five years after diagnosis and a high risk of transformation (PMID: 14508396, 24100447, 31396979). Recent studies have also demonstrated overlapping mutational landscape among classic Hodgkin lymphoma, NLPHL and DLBCL (PMID: 40670673), highlighting importance of integrated clinicopathologic assessment. Although molecular study was not performed due to patient's financial restriction, isolated axillary mass, absence of systemic or bone marrow involvement, and focal area reminiscent of NLPHL pattern A support a diagnosis of NPLHL, E pattern. CD15 positive LP cells are infrequent but have been reported [PMID: 21457163], and may correlate with more aggressive nature, worthy of exploration. Pattern E and areas of necrosis are also of concern for a more aggressive clinical course.

Panel Diagnosis: NLPB/HL

EA4HP26-LYWS-191

Mantle cell lymphoma with florid granulomatous reaction

Dr. Gioia Di Stefano¹, Dr. Massimo Granai², Prof. Stefano Lazzi², Prof. Raffaella Santi³

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Case Description

A 63-year-old man with no significant medical history presented with left axillary and submandibular lymphadenopathy. Whole-body CT and PET/CT revealed widespread supra- and subdiaphragmatic hypermetabolic lymphadenopathy, including a bulky left axillary mass. The patient reported no B symptoms, and an excisional biopsy of the left axillary lymph node was performed.

Biopsy Fixation Details

Fixed in 10% neutral buffered formalin and paraffin-embedded (FFPE).

Frozen Tissue Available

Not performed.

Details of Microscopic Findings

Histological examination showed a population of mature lymphocytes with follicular architecture. Mantle areas were expanded by small to medium size lymphoid cells with scant cytoplasm and slightly irregular nuclear contours

resembling centrocytes. Moreover, the germinal centers were effaced by well-formed granulomas composed of epithelioid histiocytes and occasional Langhans-type giant cells, with focal coagulative necrosis.

Immunophenotype

By immunohistochemistry, the small-medium sized lymphoid population was CD20+, CD5-/+, CyclinD1+, Sox11+, Bcl2+, CD10-, Bcl6-, CD3-, with a Ki67 proliferation index of 30-40%. EBV EBER was negative.

Cytogenetics

Not performed.

Molecular Studies

Polymerase Chain Reaction (PCR) for mycobacterial DNA and serological analysis for *Toxoplasma gondii*, *Leishmania* spp, *Bartonella henselae*, Cytomegalovirus and Epstein-Barr virus were negative.

Proposed Diagnosis

Mantle cell lymphoma (MCL) with a prevalent mantle zone growth pattern associated with a non-specific granulomatous cell reaction.

Interesting Feature(s)

After staging, the disease was classified as stage IIIA, high-risk according to the MIPIb. Although high-risk based on clinical-pathobiological features, the disease exhibited a non-aggressive course. We hypothesize that the prominent granulomatous tumour microenvironment, possibly mediated by macrophages, may have contributed to this favourable outcome. At follow-up, the patient remains disease-free after first-line chemotherapy and rituximab maintenance. This case highlights a mantle cell lymphoma characterized by extensive granulomatous involvement of the germinal centers, thereby expanding the spectrum of granuloma-associated lymphomas.

Panel Diagnosis: MCL w/granulomas

EA4HP26-LYWS-192

Nodular lymphocyte predominant Hodgkin lymphoma with extensive pattern E

Dr. Elizaveta Flerova, Dr. Linda Dao

Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, USA

Case Description

32-year-old male with prior medical history of hypercholesterolemia and obesity presented with right axillary lymphadenopathy. PET scan demonstrated stage IV disease with intensely FDG avid right supraclavicular and right axillary lymphadenopathy (SUV max of 29.9), splenomegaly (15.8 cm) with multifocal uptake in the spleen (SUV of 14.7), multiple hepatic lesions, peripancreatic and pericardial lymphadenopathy, osseous lesions in the left femoral shaft and right T5 transverse process.

Following the diagnosis, patient started on R-CHOP. He had good response by PET after 3 cycles of chemotherapy and is currently continuing treatment.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Excisional biopsy of the right cervical lymph node showed enlarged lymph node with architecture effaced by diffuse lymphohistiocytic infiltrate. The infiltrate was composed of small lymphocytes, epithelioid histiocytes, and admixed LP (lymphocyte-predominant) cells. LP cells were present individually without forming aggregates or sheets. LP cells showed multilobated nuclei, pale chromatin, and prominent nucleoli. Histiocytes were present in small aggregates

and individually. Some histiocytic aggregates were associated with LP cells, while others were admixed with small background lymphocytes.

Immunophenotype

LP cells showed preserved B-cell program and were positive for CD20, CD19 (weak), CD45, BOB1, MUM1 (subset weak partial), OCT2, PAX5 (variable), MEF2B. They were negative for ALK, CD30, CD15, and EBER. CD3 highlighted abundant T-cells in the background that were forming rosettes around the LP cells. T-cells rosettes were positive for PD-1 and MUM1. A subset of T-cells was positive for CD57 with no clear rosette formation. IgD and CD23 highlight rare small residual mantle zone B-cells. CD68 showed increased histiocytes. CD21 was predominantly negative with minute focus of residual follicular dendritic cell meshworks. There were rare small EBER positive cells consistent with latent infection.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Nodular lymphocyte predominant B-cell lymphoma (ICC) / Nodular lymphocyte predominant Hodgkin lymphoma (WHO5). Pattern E involving >95%.

Interesting Feature(s)

1. This case is an example of a rare pattern E of NLPHL involving >95% of lymph node.
2. Background is composed of abundant T-cells and histiocytes with no distinct nodularity. Aggregates of epithelioid histiocytes were associated with both LP cells and small background lymphocytes, forming a complex microenvironment.
3. The differential diagnosis with T-cell histiocyte rich large B-cell lymphoma (THRLBCL) is challenging. The presence of residual IgD+ mantle cells, an abundant population of T cells expressing TFH markers with rosettes around neoplastic B lymphocytes, and rare foci of FDC meshworks, favor NLPHL over THRLBCL.
4. This case showed near-complete absence of FDC meshworks. Rare focal CD21 positivity underscores the importance of extensive sampling.
5. In addition to TFH phenotype, T-cell rosettes were positive for MUM1. MUM1 can be expressed in activated T-cells, but its expression was not systematically studied in T-cell rosettes of NLPHL. In one study, MUM1-positive T-cell rosettes were more frequent in AITL with HRS-like cells than cHL (PMID: 26617862).
6. Patient showed good treatment response despite advanced clinical stage at presentation.

Panel Diagnosis: NLPB/HL

EA4HP26-LYWS-207

T-cell histiocyte rich large B-cell lymphoma with CD30 expression

Dr. Andrew C. Cook, Dr. Fatima Khan, Dr. Amer Wahed, Dr. Andy Nguyen, Dr. Jacob Armstrong, Dr. Hanadi El Achi, Dr. Brenda Mai

University of Texas Health Science Center at Houston, Pathology and Laboratory Medicine, Houston, USA

Case Description

19-year-old male with right pelvic and inguinal lymphadenopathy.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

None

Details of Microscopic Findings

Rare scattered large malignant atypical lymphocytes (<10%) in a background dominated by abundant small lymphocytes and histiocytes that obscure the neoplastic cells

Immunophenotype

Positive: CD20, PAX5, CD30, BCL6 (weak), C-MYC (weak), MUM1 (subset), Ki-67 (~90%)

Negative: CD5, CD10, CD15, BCL2, Cyclin D1, ALK1, EBERISH

Concurrent flow cytometry shows predominantly a T-cell population (98% of the total lymphocytes with an elevated CD4:CD8 ratio of 11.8. B-cells were not identified by flow cytometry.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

CD30-positive T-cell/histiocyte-rich large B-cell lymphoma (TCHRLBCL)

Interesting Feature(s)

The rare scattered large cells showed strong CD20 and PAX5 expression but were negative for CD15, ALK1, and EBER ISH with a background of small T-cells and histiocytes, supporting the diagnosis of a T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) versus a classic Hodgkin lymphoma (CHL) or a T-cell lymphoma such as peripheral T-cell lymphoma (PTCL) or anaplastic large T-cell lymphoma (ALCL).

THRLBCL can be polymorphic with an abundant amount of histiocytes, small lymphocytes, and plasma cells, requiring careful diagnosis.

This case is interesting in that it also has expression of CD30 which is generally not seen in THRLBCL; the expression of CD30 caused confusion with a diagnosis of CHL and a PTCL however both were excluded due to the strong CD20 expression and the lack of CD3 expression.

CD30-positive THRLBCL describes a challenging lymphoma case where large B-cells in a T-cell/histiocyte-rich background express the CD30 marker, complicating diagnosis and treatment, but also potentially opening doors to targeted therapies.

Panel Diagnosis: Lymphoma consistent with THRLBCL in a limited core biopsy sample

EA4HP26-LYWS-220

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)

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¹ University of British Columbia, Pathology and Laboratory Medicine, Vancouver, Canada; ² BC Cancer, Pathology and Laboratory Medicine, Vancouver, Canada

Case Description

A 52-year-old man presented with a 3-month history of fatigue, weight loss, night sweats, pancytopenia and hypercalcemia. CT imaging showed extensive lymphadenopathy above and below the diaphragm, as well as marked splenomegaly (32 cm) and solid masses in the liver (up to 1.4 cm). An excisional biopsy of a right inguinal lymph node was performed.

Biopsy Fixation Details

The biopsy contained two block-like resections of soft spongy nodal tissue measuring 2.5 and 2.0 cm in greatest dimension. The specimen was fixed in 10% of Neutral Buffered Formalin for approximately 24 hours before processing. Representative fresh tissue was also submitted for flow cytometry.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The lymph node showed complete architectural effacement by an extensive atypical lymphohistiocytic proliferation in a diffuse pattern. Lymphocytes were predominantly small and mature in appearance and admixed with abundant reactive appearing histiocytes. There were also few scattered atypical large lymphocytes with oval/bilobed nuclei, vesicular chromatin with prominent nucleoli and scant cytoplasm. No follicular architecture was identified.

Immunophenotype

By immunohistochemistry, the large atypical cells were B-cells positive for CD20, CD79a, PAX5, CD19 and CD45, with co-expression of BCL6, MUM1 and CD30(weak). The large cells were negative for CD10, CD5, Cyclin D1, IgD, CD23, EMA, CD15, EBER(ish), ALK and cytokeratins. Ki67 highlighted the great majority of the large cells. No significant population of small B-cells were identified. Small lymphocytes were CD3+ T-cells which showed extensive staining for PD-1, yet did not form rosettes surrounding the large B-cells. CD68 identified abundant histiocytes which showed extensive staining for PD-L1. No follicular dendritic cell meshworks were identified by CD21 or CD23 immunostains.

Flow cytometry showed too few B-cell to assess clonality (<1% of events). However, a supplementary B-cell tube showed a minor population of high forward- and side-scatter CD19+ B-cells with aberrant loss of HLA-ABC. T-cells showed no immunophenotypic abnormalities.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

The proposed diagnosis is T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL).

Interesting Feature(s)

An interesting histologic feature of this case was the extensive lymphohistiocytic infiltrate which masked the presence of rare abnormal large lymphocytes. The infiltrate was thought to be benign before specialized lymphoma pathology consultation. Expression of weak CD30 by the large B-cells is also an uncommon feature in THRLBCL. Extensive expression of PD-1 and PD-L1 within the lymphoma, as well as loss of HLA-ABC by the abnormal B-cells suggests immune evasion as an important driver of malignancy in this case. THRLBCL is characterized by a typically aggressive clinical course. This lymphoma was refractory to both R-CHOP and R-ICE chemoimmunotherapy, with extensive nodal and extranodal involvement on post-treatment imaging. The patient expired one year after diagnosis.

Panel Diagnosis: THRLBCL

Large B-cell lymphoma with a lymphocyte and histiocyte rich microenvironment: a diagnostic dilemma

PhD/MD Sehbali Arslankoz¹, PhD/MD John R. Goodlad²

¹ Ankara Etlik City Hospital, Pathology, Ankara, Turkey; ² NHS Greater Glasgow and Clyde, Pathology, Glasgow, UK

Case Description

An 18-year-old female presented with generalized lymphadenopathy. PET-CT demonstrated avid nodes above and below the diaphragm, with extranodal involvement of liver, spleen, kidneys and skeleton.

A left cervical lymph node was excised. Based on the pathological and clinical findings, the patient was treated with six cycles of R-CHOP chemotherapy followed by two cycles of methotrexate. End-of-treatment PET-CT demonstrated a complete metabolic response. At the most recent assessment, the patient remains clinically well and disease-free after approximately five years of follow-up.

Biopsy Fixation Details

10% buffered formalin.

Frozen Tissue Available

NA.

Details of Microscopic Findings

The nodal architecture was replaced by an infiltrate composed predominantly of small to intermediate lymphocytes and numerous histiocytes. There were also individually scattered large lymphoid cells with abundant cytoplasm, vesicular chromatin and prominent nucleoli, including LP-like and RS-like cells.

Immunophenotype

The large lymphoid cells had the following phenotype:

- Positive: CD20, CD79a, PAX5, OCT2, BOB1, MUM1/IRF4, BCL2 and BCL6. Focal expression of EMA and CD75.
- Negative: CD10, CD15, CD23, CD30, cyclin D1, EBV (LMP1 and EBER-ISH).

The background small lymphocytes were predominantly T cells with no loss of CD2, CD3, CD5 or CD7. Most expressed CD8, TIA1 and granzyme B. Few CD57 or PD1 positive T-cells were seen and no well-formed T-cell rosettes were identified. Staining with antibodies to CD21 and CD23 demonstrated an absence of FDC meshworks.

Cytogenetics

NA.

Molecular Studies

NA.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma according to current criteria but may be better regarded as an aggressive variant nodular lymphocyte predominant B cell lymphoma / nodular lymphocyte predominant Hodgkin lymphoma.

Interesting Feature(s)

This case highlights the overlap between some cases of nodular lymphocyte predominant B cell lymphoma/nodular lymphocyte predominant Hodgkin lymphoma (NLPBL/HL) and T-cell/histiocyte-rich large B-cell lymphoma (THRLBL). The presence of at least a single nodule and background T-cells expressing CD4, CD57 and/or PD1, often with formation of rosettes around large LP cells, is said to favour the former. Conversely, a purely diffuse growth pattern and predominance of cytotoxic T-cells in the background is thought more indicative of THRLBL. Although the young age of our patient is more in keeping with NLPBL/HL, the presence of widespread disease and pathological features are more typical of THRLBL as currently defined.

However, cases of typical NLPBL/HL may progress to a THRLBL-like growth pattern and NLPBL/HL pattern E is associated with a shift in the tumour microenvironment toward a THRLBL-like immune contexture, including

enrichment of cytotoxic T-cell populations. Gene expression profiling also reveals overlapping tumour-cell transcriptional profiles across typical NLPBL/HL, THRLBL-like NLPBL/HL and THRLBL, with differences driven predominantly by the tumour microenvironment rather than the neoplastic cells (PMID: 37854674, PMID: 24244368; PMID: 34208705). Moreover, recurrent mutations of certain genes (*JUNB*, *DUSP2*, *SGK1*, *SOCS1*, *CREBBP*) are seen at similar frequencies in NLPBL/HL and THRLBL (PMID: 30213827). These findings indicate that it may be more appropriate to consider NLPBL/HL and THRLBL part of the same biological spectrum rather than two distinct entities which would explain the dichotomy between young age and histological appearances in our patient.

Panel Diagnosis: THRLBCL vs. aggressive NLPB/HL

EA4HP26-LYWS-228

EBV-positive diffuse large B-cell lymphoma, NOS, with T-cell/histiocyte-rich large B-cell lymphoma-like morphology

PhD/MD Sehbali Arslankoz¹, PhD/MD John R. Goodlad²

¹ Ankara Etlik City Hospital, Pathology, Ankara, Turkey; ² NHS Greater Glasgow and Clyde, Pathology, Glasgow, UK

Case Description

A 72-year-old male presented with enlarged neck nodes. PET-CT scan demonstrated bilateral cervical lymphadenopathy extending into the left supraclavicular region, with no disease elsewhere. Clinical and laboratory assessment did not indicate immune dysregulation; the patient had neither a history of autoimmune disease nor exposure to immunosuppressive therapy, and HIV serology was negative.

A core biopsy of a left cervical lymph node was performed. Based on the pathological findings, the case was managed as Epstein–Barr virus (EBV)–positive diffuse large B-cell lymphoma, NOS (EBV+ DLBCL), and the patient was treated with six cycles of R-CHOP chemotherapy. End-of-treatment imaging demonstrated a complete metabolic response. At follow-up, the patient remained clinically well and was discharged from routine haematology care three years after presentation.

Biopsy Fixation Details

The biopsy was fixed in 10% buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The nodal architecture was partially effaced by a diffuse infiltrate of small lymphocytes, plasma cells, and numerous histiocytes. The histiocytic component was prominent and frequently formed small, non-caseating epithelioid granulomas, contributing to an immune-rich background. There was also a minor population of individually distributed large lymphoid cells. These possessed moderate to abundant cytoplasm with large, pleomorphic nuclei and prominent nucleoli, some resembling Reed–Sternberg cells or mononuclear variants.

Immunophenotype

The large atypical tumour cells had the following phenotype:

- Positive: CD19, CD20, CD22, CD30, CD79a, PAX5, OCT2 (strong, uniform), BOB1, IRF4/MUM1, BCL6, MYC protein. In situ hybridization for EBV (EBER) and immunohistochemistry for LMP1 were positive within the tumour cells, but staining for EBNA2 was negative (type II latency).
- Negative: CD3, CD15.

The background small lymphocytes were predominantly CD3-positive T lymphocytes.

Cytogenetics

No *MYC* or *IGH::MYC* rearrangement was detected.

Molecular Studies

No additional molecular studies were performed.

Proposed Diagnosis

Epstein–Barr virus–positive diffuse large B-cell lymphoma, NOS, with a T-cell/histiocyte-rich large B-cell lymphoma–like growth pattern.

Interesting Feature(s)

This case highlights the diagnostic challenge posed by EBV+ DLBCL presenting with an immune-rich microenvironment and a low tumour cell burden. In reported series of EBV+ DLBCL, a T-cell/histiocyte-rich large B-cell lymphoma–like growth pattern has been described as a frequent morphological presentation, particularly in younger patient cohorts (Nicolae et al., 2015; PMID: 25999451). Such cases may closely mimic classical Hodgkin lymphoma because of the polymorphic inflammatory background, the sparse distribution of large atypical cells and frequent CD30 expression, a phenomenon that is well recognised in the literature (Bosch-Schips et al., 2022; PMID: 35159009). Distinction from EBV-positive classical Hodgkin lymphoma relies on careful assessment of the neoplastic cell population, with preservation of the B-cell programme, including expression of CD20 and B-cell–specific transcription factors such as OCT2 and BOB1, together with heterogeneity of EBV marker expression, supporting classification within the spectrum of EBV+ DLBCL rather than classical Hodgkin lymphoma (Asano et al., 2009; PMID: 19075188).

Panel Diagnosis: EBV+ DLBCL

EA4HP26-LYWS-229

Primary Bone Marrow Presentation of a rare case of T-Cell/Histiocyte-Rich Large B-Cell Lymphoma: A Diagnostic Challenge.

Prof. Samah Kohla^{1,2}, Dr. Feryal Ibrahim¹, Dr. Ibrahim Ganwo¹, Dr. Amna Gameil^{3,2}, Dr. Sarah ElKourashy^{3,2}, Dr. Samah Kohla, as the presenting and first author, established the diagnosis and authored the abstract. The diagnostic findings were reviewed by Dr. Fera Ibrahim, while the abstract was reviewed by Dr. Ibrahim Ganow and Dr. Amna Gameil. Case management was carried out by Dr. Sarah Alkourashy.

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Case Description

A 35-year-old man presented with B symptoms. PET-CT showed generalized FDG-avid lymphadenopathy with bulky abdominal and pelvic nodal masses and diffuse increased FDG uptake in the bone marrow, raising suspicion for marrow involvement. A pelvic mass core biopsy was highly suspicious for lymphoma. The patient subsequently developed pancytopenia, prompting bone marrow examination.

Biopsy Fixation Details

Bone marrow aspirate, touch imprints, clot section, and trephine biopsy were obtained from the right posterior iliac crest. The trephine biopsy consisted of two fragmented cores measuring an aggregate length of 2.4 cm and was fixed in formalin and decalcified.

Frozen Tissue Available

No frozen tissue was available.

Details of Microscopic Findings

Bone marrow aspirate was cellular with trilineage hematopoiesis, prominent erythropoiesis with dyserythropoietic features, and no increase in blasts. Lymphocytes were not increased. Numerous histiocytes with focal

hemophagocytosis were identified. The trephine biopsy showed two patterns. One fragment was normocellular for age (60–70%) with preserved trilineage hematopoiesis. The second fragment was hypercellular (75–90%) and showed extensive infiltration by scattered pleomorphic large atypical cells, including Hodgkin-like forms, embedded in a background rich in small lymphocytes and numerous histiocytes, with suppression of normal hematopoiesis. Reticulin stain demonstrated mild to moderate fibrosis in involved areas (MF 1–2).

Immunophenotype

The large atypical cells expressed CD20, PAX5, CD79b, BCL6, MUM1 (variable), and EMA. Rare cells were CD30 positive; CD15 was negative. EBV (EBER) was negative. The background population consisted predominantly of CD3+, CD5+ T cells with CD4 predominance and diffuse PD-1 expression. Numerous histiocytes were highlighted by CD68 and CD163. CD23 was negative.

Flow cytometry showed ~2% polytypic T cells and <0.1% B cells without evidence of a monotypic B-cell population.

Cytogenetics

Conventional karyotyping showed a normal male karyotype (46,XY). Interphase FISH studies for BCL6, MYC, and IGH/BCL2 rearrangements were normal.

Molecular Studies

No molecular studies were performed.

Proposed Diagnosis

Bone marrow involvement by **T-cell/Histiocyte-Rich Large B-Cell Lymphoma (TCHRLBCL)**.

Interesting Feature(s)

This was a diagnostically challenging case in which the **definitive diagnosis was established on bone marrow biopsy rather than lymph node tissue**, despite extensive nodal disease on PET-CT. The neoplastic B cells were extremely sparse and masked by a prominent T-cell and histiocytic infiltrate, leading to non-diagnostic flow cytometry. The findings closely mimicked classical Hodgkin lymphoma and reactive marrow processes, underscoring the importance of trephine biopsy morphology, immunohistochemistry, and clinicoradiologic correlation in recognizing TCHRLBCL when bone marrow involvement is the initial or dominant manifestation.

Panel Diagnosis: Large B cell lymphoma consistent with THRLBCL in a bone marrow biopsy

EA4HP26-LYWS-230

T-cell/histiocyte-rich large B-cell lymphoma

Dr. Nives Zimmermann, Dr. Youssef Khafateh

University of Cincinnati, Pathology and Laboratory Medicine, Cincinnati, Germany

Case Description

The patient is a 69-year-old Black male with history of prostate adenocarcinoma (Gleason 3+4, diagnosed in 2024, treated with radical prostatectomy). He presented with weight loss and weakness, and was found to be undergoing spontaneous tumor lysis syndrome (with acute kidney injury and hypercalcemia). CT scan showed diffuse lymphadenopathy and splenic lesions.

Following the diagnostic biopsy (described below), the patient was staged as stage III, and treated with R-CHOP. PET scan for treatment response assessment had not occurred at time of case submission.

Biopsy Fixation Details

Formalin-fixed, paraffin embedded.

Frozen Tissue Available

Not available (clinically, diagnosis of metastatic carcinoma was suspected and thus all tissue was submitted for FFPE)

Details of Microscopic Findings

Histologic sections show a proliferation consisting of small lymphocytes, prominent histiocytes, and scattered large atypical cells.

Immunophenotype

By immunohistochemistry, the small lymphocytes are predominately CD3 positive T cells. The histiocytes stain uniformly for CD163. The large atypical cells are positive for CD20 and CD45 and negative for CD3, CD30, CD138, SOX10, CAM 5.2, and pankeratin. CD21 and CD23 failed to reveal any follicular dendritic cell meshworks. *In situ* hybridization for EBER is negative. Controls stained appropriately.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

- T-cell/histiocyte-rich large B-cell lymphoma.

Interesting Feature(s)

The interesting feature of this case is that its clinical presentation and initial histologic assessment were suspecting metastatic carcinoma.

Panel Diagnosis: NLPB/HL

EA4HP26-LYWS-240

Histiocyte-rich, EBV-positive diffuse large B-cell lymphoma preceding angioimmunoblastic T-cell lymphoma by 4 years.

Prof. Luisa Lorenzi^{1,2}, PhD/MD Marco A. Cocchi¹, Dr. Giulio E. Mandelli², Dr. Flavia Melotti², Dr. Mattia Facchetti², Dr. Iacopo Ghini², M.Sc./M.A. Silvia Lonardi^{1,2}, M.Sc./M.A. Emma Albertini², M.Sc./M.A. Daniela Medicina², Dr. Piera Balzarini^{1,2}, Dr. Matteo Fusi¹, Dr. Chiara Pagani³

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Case Description

In November 2011, a 68-year-old immunocompetent man presented to the hematologist for systemic symptoms and multiple lymphadenopathies above and below the diaphragm. Surgical excision of a right axillary lymph node was performed, yielding a diagnosis of EBV-positive diffuse large B-cell lymphoma of the elderly (WHO 4). Bone marrow biopsy was negative for disease. The patient completed 6 cycles of R-CHOP(14) and achieved a complete response by the end of therapy. In December 2015 (48 months after the initial diagnosis), the patient presented with PET-positive splenic lesions and left cervical adenopathy. Suspecting disease relapse, surgical resection of a left cervical lymph node was performed and Angioimmunoblastic T-cell lymphoma (AITL) with EBV-positive large B-cells was detected. GemOD therapy was administered, but the patient died of disease during treatment.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

Yes

Details of Microscopic Findings

Multiple fragments of lymph node were sent for histological analysis and showed parenchyma diffusely effaced by a polymorphic infiltrate including numerous small, non-atypical, T-cell lymphocytes, histiocytes, some with tangible

bodies macrophages appearance, and large atypical B-cells. The latter were heterogeneously distributed and confluent in large sheets in some of the fragments. Numerous mitoses were evident (22/10 HPF).

Immunophenotype

Large and atypical B cells showed expression of CD20, MUM1, OCT2 and BOB1, PAX5 was weakly positive, only partial expression of CD79a and Bcl6 was detected. CD30 was expressed at variable intensities and no expression of CD10, CD138 nor light chains were detected. Both Bcl2 and c-Myc were intensively positive in a wide fraction of these atypical cells. All of the latter were positive for EBV/EBER and EBV-LMP1; RNAscope revealed transcript of EBNA2, indicating an EBV latency program III. Small T lymphocytes were positive for CD2, CD3, CD5, with equal CD4/CD8 distribution, they partially expressed ICOS and Bcl6 but resulted negative for CD10, PD1 and only few expressed CXCL13. No FDC network was evident at CD21 stain.

Cytogenetics

No rearrangements on *MYC*, *BCL2*, *BCL6* were detected by FISH.

Molecular Studies

BCR clonality: IGH FR1: no signal; FR2 and FR3: polyclonal with repertoire restriction; IGkA and IGkB: clonal on polyclonal background. **TCR clonality:** dominant picks on polyclonal background. **NGS (targeted panel 73 genes):** the following pathogenic mutations were identified: *BIRC3*^{R401K} (VAF 47.6%), *STAT6*^{N503S} (VAF 47%), *TET2*^{C1273S} (VAF 32.6%), *CD58*^{c.628G>A} (VAF 6.9%), *EP300*^{N1236K} (VAF 4.8%). Of these, the first three were detected also in the AITL (2016).

Proposed Diagnosis

EBV+ diffuse large B cell lymphoma with rich histiocytic and T-cell infiltrate, carrying CHIP-related mutations, anticipating angioimmunoblastic lymphoma.

Interesting Feature(s)

The association of angioimmunoblastic T-cell lymphomas with EBV-positive proliferations is well known and reported, however, B lymphomas anticipating AITL are uncommon. The time *spread* among these two diseases was also unusually long for this patient. In our opinion, the submitted case did not show sufficient morphological features to rise the suspect of a latent Tfh clone (no FDC expansion, no atypical T cells, no *RHOA* mutations). The richness of the microenvironment and the molecular evidence of a pathogenic *TET2* variant, often associated with clonal hematopoiesis, could have had a role in the pathogenesis of this sequence of events. EBV lat-III may rise the suspicion of immune impairment, however, little is known on EBV latency in AITL.

Panel Diagnosis: EBV+ DLBCL with atypical T-cell population (CHIP related mutations) evolving to AITL

EA4HP26-LYWS-243

T-cell/histiocyte-rich large B-cell lymphoma followed by sarcoid-like reaction

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Case Description

A 26-year-old male patient was referred to our hospital due to progressive fatigue, involuntary weight loss, painless supraclavicular lymphadenopathy and headaches. Blood tests showed slightly elevated LDH (300 U/L), mild leucopenia (2.4G/L) and thrombocytopenia (135.000/μL), microcytic anemia (Hb 127g/L) and upper urinary tract infection by *E. coli*. The patient had a history of vesico-ureteral reflux and neurogenic bladder due to a compressive dorsal lipoma. PET-CT showed hepatomegaly (18 cm), extensive supra- and infradiaphragmatic lymphadenopathy

(SUVmax 49) with contiguous infiltration of the cervical muscles and vertebrae, and multiple hypermetabolic masses in the spleen, subcutaneous tissue and possibly lungs. Whole-body MRI revealed diffuse involvement of the axial skeleton. A surgical biopsy of the supraclavicular lymphadenopathy was performed. Bone marrow biopsy showed no evidence of lymphoma. The patient was treated with 4 cycles R-ACVBP, 3 cycles of high dose Methotrexate and consolidation by R-Ifos-VP16, followed by Ara-C. Autologous stem cell transplant was not performed because of impaired cardiac function, attributed to Doxorubicin and Rituximab administration. During the follow-up, recurrence was suspected based on progressive lymphadenopathy and a micronodular infiltration of the lungs on PET-CT. However, subsequent biopsies revealed necrotising granulomas in the lungs consistent with a sarcoid-like reaction. Lymph node excision showed non-specific reactive changes without lymphoma. Currently, the patient is considered disease-free 5 years of diagnosis.

Biopsy Fixation Details

Neutral buffered formalin

Frozen Tissue Available

None available

Details of Microscopic Findings

Lymph node architecture was obliterated by a diffuse, polymorphous infiltrate of histiocytes, small lymphocytes and scattered large, blastic cells with elongated, sometimes reniform nuclei and variably sized nucleoli, which appeared central or peripheral, resembling centroblasts or rarely LP cells. Mitoses were overall scarce but focally grouped and there were small areas of necrosis within the histiocytic component, without granuloma formation. There were no Reed-Sternberg cells, no residual follicles or nodular patterns suggestive of nodular lymphocyte predominant B-cell lymphoma.

Immunophenotype

B-cell markers (CD20, PAX5, CD79a) were strongly expressed in the atypical cells and showed near absence of B lymphocytes in the background, which consisted of predominantly CD4+ T cells, including a PD1+ TFH population, only rarely forming rosettes around the atypical cells. The latter were positive for CD45, BCL2, BCL6, MUM1 (variable intensity), MYC and Kappa, partially positive for CD15 and EMA, and very rarely CD30+. There were no dendritic networks (CD21, CD23) and no residual follicle mantles (IgD). EBER was negative.

Cytogenetics

Not performed

Molecular Studies

Clonality analysis by PCR (Biomed-2) showed a clonal IGH rearrangement. No TCRG gene rearrangement was detected.

FISH analysis (ZytoLight® SPEC Break Apart Probe) demonstrated a *BCL6* rearrangement in the large atypical cells. No rearrangement of *BCL2* or *MYC* was found.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma (with *BCL6* rearrangement)

Interesting Feature(s)

This case illustrates a THRLBCL with *BCL6* rearrangement and unusual CD15 expression, raising the differential diagnosis with classical Hodgkin lymphoma; however, the morphology and strong expression of B-cell markers helped exclude that hypothesis. Furthermore, the follow-up was marked by a sarcoid-like reaction involving the lungs, causing clinical uncertainty regarding lymphoma recurrency.

Panel Diagnosis: THRLBCL

From Indolent to Aggressive disease: Transformation of Nodular Lymphocyte Predominant Hodgkin Lymphoma to T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

Dr. Forough Sargolzaeiaval, Prof. Jonathan W. Said, [Dr. Sheeja Pullarkat](#)

University of California Los Angeles, Pathology and Lab Medicine / Hematopathology, Los Angeles, USA

Case Description

The patient is a 50-year-old male with a history of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) diagnosed in 2012 after excisional biopsy of a left axillary mass. He received two cycles of Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) (completed 01/2013) followed by involved-field radiation therapy, complicated by cytopenias and transient hepatic and renal dysfunction, and achieved complete metabolic remission on PET/CT in 2013. From 2013–2017, he had intermittent thrombocytopenia and pulmonary nodules identified in 2015 during evaluation for syncope/shortness of breath, without confirmed lymphoma recurrence. In 2017, he developed ~10-lb weight loss and low-grade fevers; PET/CT (12/2017) demonstrated FDG-avid abdominal/pelvic/cervical/supraclavicular lymphadenopathy, hepatosplenomegaly with FDG-avid lesions, and diffuse osseous uptake. Bone marrow biopsy (01/2018) was normocellular without lymphoma involvement, with normal karyotype and negative FISH/NGS. A left supraclavicular lymph node biopsy confirmed recurrent NLPHL (CD20+, strong PAX5+, OCT2+, BOB1+; CD30–, CD15–, EBV–), and he was treated with bendamustine/rituximab for 6 cycles. He later developed progressive biliary strictures and progressive splenic disease, and PET/CT in 2023 showed new FDG-avid hepatic lesions, large splenic masses, retroperitoneal and hilar lymphadenopathy, and an FDG-avid osseous focus.

Biopsy Fixation Details

Tissue fragments were fixed in 10% neutral buffered formalin with a minimum tissue-to-formalin ratio of 1:5 for up to 24 hours.

Frozen Tissue Available

NA

Details of Microscopic Findings

Examination demonstrated multiple fragments of splenic parenchyma with effacement of normal white and red pulp architecture, extensively replaced by a diffuse lymphoid infiltrate. The background population was composed predominantly of small reactive-appearing T lymphocytes and numerous histiocytes. Scattered large atypical lymphoid cells were present as isolated cells or small clusters and exhibited irregular nuclear contours, vesicular chromatin, prominent nucleoli, and moderate pale cytoplasm. Well-formed follicles were not identified.

Immunophenotype

Concurrent flow cytometry showed no monotypic B-cell population and no discrete pan-T-cell aberrancy. By immunohistochemistry, the scattered large atypical cells were positive for PAX5, CD79a, BCL2, BCL6, and MUM1, with kappa light chain restriction, and were negative for CD19, CD20, CD30, and EBV-EBER by in-situ hybridization.

Cytogenetics

NA

Molecular Studies

NA

Proposed Diagnosis

Consistent with T-cell and histiocyte- rich large B-cell lymphoma (THRLBCL). The specimen contains no areas with NLPHL fan patterns A-D, and thus is best classified as THRLBCL, and may suggest transformation of NLPHL.

Interesting Feature(s)

This case highlights the recognized biologic and morphologic continuum between NLPHL and THRLBCL, in which related tumor cells may be accompanied by a shifting, T-cell/histiocyte-rich microenvironment. The splenic biopsy demonstrates the classic THRLBCL pattern of diffuse effacement by abundant T cells and histiocytes with only scattered neoplastic B cells, creating a diagnostic “needle-in-a-haystack” challenge. It also underscores a practical pitfall: THRLBCL-like patterns (including Fan pattern E/F in NLPHL) can be difficult to distinguish from overt transformation on limited sampling. Clinically, the decade-long relapsing course with late, aggressive splenic and extranodal disease contrasts with the typically indolent behavior of NLPHL and supports biologic progression along this spectrum.

Panel Diagnosis: Favor NLPB/HL

EA4HP26-LYWS-266

EBV-Positive T-Cell/Histiocyte-Rich Large B-Cell Lymphoma in a Lung Transplant Recipient

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UTHealth Houston (The University of Texas Health Science Center at Houston), Department of Pathology and Laboratory Medicine, Houston, Texas, Germany

Case Description

66-year-old male with prior history of lung transplant presenting with a new lung mass and mediastinal lymphadenopathy.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

Not performed

Details of Microscopic Findings

Histologic sections show lung tissue with atypical lymphoid infiltrate. The atypical lymphocytes are large in size, show moderate amount of eosinophilic cytoplasm, round to irregular nuclear contours, and clumped chromatin.

Immunophenotype

The atypical lymphocytes are positive for CD20, PAX-5, BCL-6 (in a small subset), C-MYC (small subset), EBV-ISH, and negative for CD5, CD15, CD10, BCL-2, Cyclin-D1. AE1/AE3 highlight the lung tissue. SOX-10, GMS, AFB are negative. CD3 demonstrate significant background small T-lymphocytes which co-express CD5. Ki67 proliferation index is high (~70%).

Cytogenetics

Not performed

Molecular Studies

Fluorescence in situ hybridization (FISH) studies demonstrate gain of the immunoglobulin heavy chain (IGH) locus at chromosome 14q and/or the presence of an IGH rearrangement, supporting the presence of a clonal B-cell lymphoproliferative process. No evidence of MYC gene rearrangement is identified by FISH analysis.

Proposed Diagnosis

T-cell histiocyte rich large B-cell lymphoma complicated by hemophagocytic lymphohistiocytosis.

Interesting Feature(s)

This patient had a T-cell histiocyte rich large B-cell lymphoma complicated by hemophagocytic lymphohistiocytosis (HLH); HLH is generally seen more in EBV-positive lymphomas or T-cell lymphomas.

EA4HP26-LYWS-267

T-cell/Histiocyte Rich Large B-cell Lymphoma in a patient with a remote history of Nodular Lymphocyte Predominate Hodgkin (B-cell) Lymphoma

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Case Description

The patient is a 44-year-old male with a history of obesity, hypertension, and type 2 diabetes mellitus with a remote history of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)/nodular lymphocyte predominant B-cell lymphoma in 2006. He was treated with four cycles of ABVD chemotherapy along with one dose of rituximab. He remained in remission with regular follow-up until 2019, when he was lost to follow-up at our institution.

In August 2025, he developed worsening urinary frequency along with progressive right lower extremity edema and right groin swelling. Imaging revealed diffuse lymphadenopathy throughout the chest, abdomen, and pelvis, including a 7.6 cm right external iliac lymph node causing mass effect on the bladder and a 5.6 cm right inguinal lymph node. An excisional biopsy of the right inguinal lymph node was performed.

Biopsy Fixation Details

Routine fixation and paraffin embedding.

Frozen Tissue Available

No frozen tissue available

6 unstained touch preparations available

Details of Microscopic Findings

The excisional biopsy of the lymph node from the right groin shows a diffusely effaced lymph node architecture with a pale, eosinophilic appearance at low power. There are numerous small lymphocytes and histiocytes as well scattered, large mononuclear cells and multi-nucleated Hodgkin/Reed-Sternberg-like (HRS-like) cells with vesicular chromatin, prominent nucleoli, and abundant cytoplasm. No nodular pattern is appreciated.

Immunophenotype

The large lymphoid cells and HRS-like cells are positive for CD20 (strong), PAX5 (strong), CD45, and BCL6 (variable), and negative for CD30, CD15, CD10, and CD23. Numerous small T-cells are highlighted by CD3 and show a mixture of CD4 and CD8-expressing cells. A subset of the T-cells express PD-1 without rosette formation around the large cells. CD68 and CD163 stains highlight numerous histiocytes. Very rare, FDCs are seen on CD21 stains with no distinct nodules. No FDC meshworks were seen on CD23 stains. EBV (EBER) ISH is negative. Ki-67 is positive in the majority of the large cells (estimated ~75%).

Flow cytometry demonstrated polytypic B cells with mixed T-cell subsets.

Cytogenetics

No growth; unsuccessful cell culture.

Molecular Studies

Not performed

Proposed Diagnosis

T-cell Histiocyte Rich Large B-cell Lymphoma

Interesting Feature(s)

1. An often-challenging differential diagnosis of T-cell/Histiocyte Rich Large B-cell Lymphoma is Nodular Lymphocyte Predominate Hodgkin Lymphoma/B-cell lymphoma, particularly pattern E. Given this patient's

history of NLPHL, this differential required careful consideration. Comparison with the original (2006) case was undertaken, and the prior NLPHL, had predominately pattern A morphology with numerous distinct B-cell nodules, and was not morphologically similar to the current case. Further, while NLPHL pattern E can entirely lack FDC meshworks, the diagnosis of this variant pattern requires the presence of at least one unequivocal NLPHL nodule. In the current case, such nodules were entirely absent, and a diagnosis of T-cell/Histiocyte-Rich Large B-cell Lymphoma was rendered.

2. ClonoSEQ B-cell Clonality (ID) was performed on the current case and identified a dominant sequence. It was also attempted on formalin fixed paraffin embedded tissue of the prior, 2006 diagnostic specimen with NLPHL; however, no dominant sequence was identified. It was thus impossible to establish or exclude a clonal relationship between the cases.

Panel Diagnosis: THRLBCL

EA4HP26-LYWS-271

Splenic Marginal Zone Lymphoma with Plasma Cell Differentiation Associated with Crystal Storing Histiocytosis

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Case Description

A 67-year-old woman consulted in our hospital derived from primary care with a constitutional syndrome and recently appeared lymphadenopathies. She had a 1-month history of epigastric pain with a feeling of bloating and weight loss of 7 kg in the last 6 months. The physical exam showed supra- and infradiaphragmatic lymphadenopathies and hepatosplenomegaly, later also confirmed by PET/CT. Laboratory findings showed normocytic anemia, thrombocytopenia, slight increase in LDH and a monoclonal IgM lambda component. The morphology in peripheral blood showed 16% of atypical lymphocytes and by flow cytometry, the cells were of B-cell lineage without a specific immunophenotype. She had a lymph node biopsy that showed a marginal zone lymphoma with plasmacytic differentiation that raised the differential diagnosis with a lymphoplasmacytic lymphoma, and a bone marrow biopsy and aspirate with similar findings as in peripheral blood. She started treatment with Rituximab monotherapy (4 cycles).

Biopsy Fixation Details

Lymph node biopsy: fixation with formalin 10%.

Frozen Tissue Available

Yes, OCT.

Details of Microscopic Findings

- **Peripheral blood:** 16% of pleomorphic, atypical lymphocytes with a regular, kidney-shaped, or sometimes irregular nucleus; semi-condensed chromatin; a single nucleolus; and relatively abundant cytoplasm with azurophilic inclusions, clasmotosis and fine extensions around the cell circumference.
- **Lymphadenopathy:** infiltration by atypical B cells with plasma cell differentiation consistent with marginal zone lymphoma and crystal-laden histiocytes.
- **Bone marrow aspirate:** 10% of lymphoid cells with similar morphology and immunophenotype to peripheral blood.
- **Bone marrow biopsy:** infiltration by approximately 20% of small lymphoid B-cells with scant cytoplasm with a nodular, interstitial and intrasinusoidal pattern.

Immunophenotype

- **Flow cytometry:** weak lambda light chain expression, CD19+, CD20 (normal+), CD22+, CD79b+, CD23 (90%+), CD305 (72%+), IgM+, CD11c (51%+), CD81 (weak+), CD95 (42%+), CD185+, CD49d+, HLA-DR+, CD27+, CD62L (62%+), CD25+, CD5-, CD38-, CD10-, CD200-, CD43-, CD31-, CD103-, CD39- and CD123-.
- **Immunohistochemistry:** B-phenotype (CD20+, CD79a+, PAX5+) with coexpression of BCL2, IgD and MNDA. Negative for CD10 and BCL6. Plasma cells (CD138+) were IgM positive and showed lambda light chain restriction. Numerous crystal-laden histiocytes (CD68 KP1 +).

Cytogenetics

FISH for BCL6 (3q27), 7q32.1 and IGH (14q32) were normal.

Molecular Studies

NGS - One pathogenic mutation in *CREBBP* with a VAF 34.4%

Proposed Diagnosis

LYMPH NODE COMPROMISED BY SPLENIC MARGINAL ZONE LYMPHOMA WITH PLASMA CELL DIFFERENTIATION ASSOCIATED WITH CRYSTAL STORING HISTIOCYTOSIS.

Interesting Feature(s)

- The lymph node morphology, the presence of an IgM monoclonal component, and the unspecific immunophenotype by flow cytometry poses the differential diagnosis between LPL and MZL.
- The presence of eosinophilic cells filled with crystals in lymph node morphology raised the discussion of whether they were plasma cells or histiocytes.
- The diagnosis was rendered because:
 - - Absence of *MYD88* mutation
 - - Presence of marked splenomegaly
 - - Morphology and immunophenotype in lymph node, peripheral blood and bone marrow aspirate.

Panel Diagnosis: SMZL with crystal-storing histiocytosis

EA4HP26-LYWS-273

Nodal T follicular helper cell lymphoma vs EBV+ Nodular lymphocyte predominant B-cell lymphoma

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Case Description

A 43-year-old man presents after self-detecting a submandibular mass while shaving. Four years prior, he had been diagnosed with EBV+ nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), stage IIA, in both nasopharynx and cervical lymph node biopsies after seeking medical advice for cervical lymphadenopathy, without other symptoms. He received treatment with ABVD and radiotherapy in 2020, achieving complete remission until the current presentation. Following a PET/CT study, a stage IIIA relapse is suggested, and a cervical lymph node is resected.

Biopsy Fixation Details

4% Formaldehyde solution (0.05M phosphate buffer) for 24-48 hours.

Frozen Tissue Available

No.

Details of Microscopic Findings

Lymph node with effaced architecture due to a mixed cellular proliferation arranged in large nodules, with some sclerotic areas. The cellularity is composed of mature lymphocytes, numerous histiocytes grouped into granulomatous structures, and occasional eosinophils. Interspersed within this cellularity are larger cells with a "Hodgkin-like" appearance, featuring large, pale, vesicular nuclei and prominent nucleoli; many of these large cells are mummified. A few preserved follicles are observed.

Immunophenotype

In the immunohistochemical study, the large cells show expression of CD20, OCT2, and CD30, along with weaker expression of CD79a, PAX5, MUM1, and BCL6; EMA expression is partial. CD15 is negative. CD10 is mostly negative in the interfollicular space (maintained within the germinal centers).

The follicular dendritic cell markers CD21 and CD23 show a nodular pattern with expanded follicles but disorganized follicular meshwork. CD3 and CD5 show abundant T-lymphocytes both in the interfollicular space and within the B-cell zones; CD4+ and CD8+ T-lymphocytes are present in similar amounts. PD1 and CXCL13 expression is relatively extensive and disorganized and seem to be expressed in atypical cells. No rosettes are identified with CD200 or CD57. Both the LMP1 immunohistochemistry and Epstein-Barr virus RNA in situ hybridization (EBER) are expressed in the large cells and in several small cells.

Flow cytometry was performed in several samples throughout the patient's study, not showing alterations with the markers studied. Peripheral blood was not evaluated, regarding the first diagnosis rendered.

Cytogenetics

Not done.

Molecular Studies

- Immunoglobulin heavy chain (IGHV) clonality analysis (CDR I, II and III): Not clonal
- T-cell receptor gene rearrangement:
 - Gamma chain: Clonal pattern in a polyclonal setting
 - Beta chain: Not clonal vs. oligoclonal
- NGS: Ongoing

Proposed Diagnosis

Nodal T follicular helper cell lymphoma, follicular type vs. Nodular lymphocytic predominant B cell lymphoma (ICC) / NLPHL (WHO HAEM 5) EBV positive

Interesting Feature(s)

This case raises the differential diagnosis between cHL, NLPBL/NLPHL and T-cell lymphoma. The literature describes cases of NLPHL with EBV positivity and an immunohistochemical profile similar to ours; however, the differential diagnosis with nodal PTCL-TFH is not thoroughly considered in such studies.

In addition, this case emphasizes the need of molecular testing in some lymphoma types to achieve a consistent diagnosis.

In our experience, CD200 may be a useful marker in the differential diagnosis between PTCL-TFH, NLPBL/NLPHL and cHL (manuscript in progress). However, we do not have cases diagnosed of EBV+ NLPBL/NLPHL in our series, and we cannot add information of such group of cases.

Panel Diagnosis: Nodal T follicular helper cell lymphoma vs EBV+ Nodular lymphocyte predominant B-cell lymphoma

Nodular Lymphocyte Predominant Hodgkin Lymphoma arising in a patient with immunodeficiency due to germline TACI / TNFRSF13B mutation

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Case Description

The patient is 55 years old man who has a history of cervical lymphadenopathy dating back to more than 5 years prior to the current diagnosis. The lymphadenopathy was biopsied by fine needle and core needle biopsy in the past 3-5 years, which revealed atypical lymphoid infiltrate, but no diagnosis of lymphoma. Additional testing revealed immunodeficiency manifested by skin allergy, normal IgG, elevated IgE, elevations of IL-10 and sIL-2R. Lymphocyte subset analysis revealed increased T cell CD4:CD8 ratio with decreased Tregs. Genetic screen revealed monoallelic TACI / TNFRSF13B mutation. Excisional biopsy of enlarged cervical lymph nodes was performed, one measuring 4.4cm and second 2.5 cm in largest dimension. Recognizing the immunodeficiency – related nature of the lymphoma the patient was treated with Rituximab monotherapy, 6 courses, with complete clinical response.

Biopsy Fixation Details

10% neutral buffered Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The architecture was effaced by nodular process with scattered large atypical cells and background comprised of predominantly small T cells. The large atypical B cells with “popcorn” and L&H cell morphology were positive for CD20, PAX5, OCT2 (strong), PAX5, BCL6, CD79a, with variable / partial MUM1, BCL2 and MYC. They were negative for CD30, EBER (EBV RNA), CD15. IgM. The small lymphocytes surrounding large lymphoma cells were predominantly CD4 positive T cells, with TFH immunophenotype positive for BCL6, PD1. The pattern of NLP is variable, nodular T cell rich and diffuse T cell Histiocyte Rich Large B cell Lymphoma - like.

Immunophenotype

Flow cytometry showed overall polytypic B cells and T cells, with increased CD4:CD8 ratio, but no aberrant immunophenotype.

Cytogenetics

Conventional karyotyping revealed normal male karyotype 46,XY.

Molecular Studies

Not performed on the lymphoma tissue. Germline mutation testing showed CFTR c.1521_1523del (p.Phe508del) heterozygous PATHOGENIC, TNFRSF13B c.542C>A (p.Ala181Glu) heterozygous Likely Pathogenic

Proposed Diagnosis

B cell lymphoma associated with inborn error of immunity, most consistent with Nodular Lymphocyte Predominant Hodgkin Lymphoma

Interesting Feature(s)

The pathophysiology of heterozygous TACI mutation leading to CVID has been shown to involve expansion of Tfh CD4 T cells and poor clearance of B cells. (Pubmed ID 24051380, "CVID-associated TACI mutations affect autoreactive B cell selection and activation" N. Romberg et al. J Clin Invest. 2013 Oct;123(10):4283-93). Conceivably, a similar mechanism could have led to development of lymphoma in this patient, characterized by predominance of BCL6 positive B cells with germinal center program and CD4 T cells positive for PD1 and BCL6 (follicular helper T

cell program). At the present time the frequency of TACI mutations and mutations affecting other elements of the BAFF / BAFFR and related pathways in Nodular Lymphocyte Predominant Hodgkin Lymphoma is unknown. Of note, BAFF (TNFSF13B) is one of the ligands for TACI and elevation of BAFF levels in serum has been reported to play a role in this variant of CVID. If BAFF (TNFSF13B) is indeed involved in the pathophysiology of the lymphoma it would create an intriguing therapeutic opportunity to use anti - BAFF antibodies currently approved for treatment of autoimmune diseases.

Panel Diagnosis: NLPB/HL, inborn error of immunity

EA4HP26-LYWS-276

Large cell transformation of follicular lymphoma with a prominent histiocyte rich background

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Case Description

A 57-year-old female presented with splenomegaly, weight loss, and night sweats. Laboratory evaluation revealed anaemia, mild thrombocytopenia, and markedly elevated lactate dehydrogenase levels. Imaging studies demonstrated marked splenomegaly and widespread FDG-avid lymphadenopathy involving nodal stations above and below the diaphragm.

An excisional biopsy of a left inguinal lymph node was performed.

Biopsy Fixation Details

Formalin-fixed (10% buffered formalin), paraffin-embedded lymph node excision biopsy.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Histological examination of the excisional lymph node biopsy showed distortion of the nodal architecture by a predominantly nodular lymphoid neoplasm, with coalescent follicles and focal areas of diffuse growth.

The neoplastic follicles were composed mainly of small lymphoid cells with centrocyte morphology, admixed with scattered larger cells showing immunoblastic/centroblastic features. In addition, focal areas showed loss of follicular architecture with diffuse growth. These areas were characterised by an increased number of large atypical cells arranged in small aggregates or short linear arrays. In the diffuse areas, atypical cells were set within an immune-rich background composed predominantly of histiocytes and small mature lymphocytes. These foci were interpreted as areas of high-grade transformation. No granuloma formation was identified.

Immunophenotype

Immunohistochemical studies demonstrated that neoplastic cells in both the follicular component and the diffuse transformed areas expressed CD20, PAX5, and BCL6, while CD10, MUM1, CD30, CD15, EMA, and ALK were negative. Bcl2 showed diffuse positivity in the low-grade follicular component and focal expression in the large cells of the transformed lymphoma. c-MYC expression was confined to the large atypical cells within the diffuse transformed areas, whereas the low-grade follicular component was negative. In addition, a subset of large atypical cells within the transformed areas showed p53 expression. Correspondingly, the Ki-67 proliferation index was low in the follicular areas and markedly increased in the large atypical cells of the diffuse component. CD23 highlighted a follicular dendritic cell meshwork displaced toward the periphery of the neoplastic follicles, while it was completely lost in the diffuse transformed areas. Epstein–Barr virus–encoded RNA (EBER) in situ hybridization was negative.

Cytogenetics

Not performed.

Molecular Studies

Fluorescence in situ hybridization (FISH) for c-MYC, BCL2, and BCL6 is pending.

Proposed Diagnosis

Follicular lymphoma with areas of transformation to diffuse large B-cell lymphoma with a prominent histiocyte- and T-cell-rich background

Interesting Feature(s)

1. This case illustrates a high-grade transformation in follicular lymphoma with a prominent T-cell and histiocyte-rich background.
2. Histiocyte-rich background probably contributes to transformation by creating a tolerogenic immune microenvironment

Panel Diagnosis: FL, transformed to DLBCL with T/Histiocyte rich background

EA4HP26-LYWS-285**Large B-cell lymphoma with a T-cell / histiocyte-rich pattern in a young patient**

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Case Description

The patient is a 22-year-old man with a history of attention-deficit/hyperactivity disorder and depression who presented with left axillary and subpectoral lymphadenopathy. Complete blood counts revealed a white blood cell count of $3.9 \times 10^9/L$, hemoglobin of 14.4 g/dL, and platelet count of $185 \times 10^9/L$. He underwent a left axillary lymph node excisional biopsy. Following the final diagnosis, he received four cycles of R-CHOP chemotherapy. At the most recent follow-up, there was no evidence of disease progression.

Biopsy Fixation Details

Sections of the lymph node were fixed in formalin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

The lymph node shows effacement of the normal architecture by a proliferation of small- to intermediate-sized lymphocytes with intermixed histiocytes/dendritic cells and scattered large atypical cells, many of which have lobulated nuclei with basophilic nucleoli.

Immunophenotype

The infiltrate was composed of scattered large atypical cells, that were positive for CD20, CD45, PAX-5, OCT-2, BOB-1(weak), and BCL-6; and negative for CD3, CD10, CD15, and CD30. EBER in-situ hybridization is negative. CD3 highlights background T cells. CD57 and PD-1 show T-cell rosettes around large cells. CD21 and CD23 show no expanded follicular dendritic cell meshworks associated with the abnormal infiltrate.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Large B-cell lymphoma with a T-cell / histiocyte-rich pattern

Interesting Feature(s)

- Multiple immunostains were performed to identify follicular dendritic cell (FDC) meshworks that could suggest an underlying nodular lymphocyte predominant Hodgkin lymphoma (NLP-HL) or one of its variant patterns. Despite the evaluation of multiple tissue sections, no FDC meshworks were identified.
- In the absence of FDC meshworks, the case meets morphologic criteria for T-cell/histiocyte-rich large B-cell lymphoma. However, given the patient's young age, the localized nodal disease confined to the left axillary region, and the presence of T-cell rosetting around large B cells, the possibility of nodular lymphocyte predominant Hodgkin lymphoma with an extensive diffuse (pattern E) growth pattern cannot be entirely excluded. Pattern E NLP-HL is well recognized to show architectural effacement, marked reduction or loss of FDC meshworks, and close morphologic and immunophenotypic overlap with THRLBCL.

Panel Diagnosis: NLPB/HL, pattern E

EA4HP26-LYWS-288

T-cell/histiocyte-rich large B-cell lymphoma with expression of T follicular helper markers.

Dr. Tran B. Nguyen¹, Dr. Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

¹ Duke University School of Medicine, Department of Pathology, Durham, USA; ² Duke Cancer Institute, Durham, USA

Case Description

The patient is a 42-year-old woman with a history of iron deficiency anemia who presented with a two-week history of night sweats, anorexia, and unintentional weight loss, and was found to have pulmonary embolism and venous thromboembolism. Imaging studies revealed breast lesions, splenic lesions, a large right-sided pelvic mass, and retroperitoneal lymphadenopathy. The right pelvic mass was biopsied and initially diagnosed as T follicular helper (TFH) cell lymphoma; however, the diagnosis was revised to T-cell/histiocyte-rich large B-cell lymphoma. Following the final diagnosis, the patient received CHOP plus rituximab chemotherapy. At the most recent follow-up, there was no evidence of disease progression.

Biopsy Fixation Details

Sections of the pelvic mass were fixed in formalin. The bone marrow core biopsy was fixed in acetic zinc formalin, followed by HCl-based decalcification.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Pelvic mass needle core biopsy: The needle core biopsy shows a diffuse lymphoid infiltrate composed of variably-sized lymphocytes with morphologic atypia. Scattered large cells were observed. Areas of necrosis are also present. Bone marrow: The bone marrow shows dense aggregates of histiocytes and T-cells with intermixed large atypical B-cells.

Immunophenotype

Pelvic mass needle core biopsy: The infiltrate consisted of variably sized lymphocytes that were positive for CD3, with apparent loss of CD5 and CD7, and showed expression of follicular helper T-cell markers (PD-1 and BCL-6). In addition, rare enlarged B cells were present and were positive for CD20 and PAX-5. EBER in situ hybridization was negative.

Bone marrow: The core biopsy shows dense aggregates of histiocytes and T-cells with intermixed large atypical B-cells with strong positivity for PAX5, BCL6, and OCT2. CD30 and CD15 are negative in lymphoma cells. PD-1 demonstrates numerous positive small lymphocytes without significant rosette formation. EBER in situ hybridization was negative.

Cytogenetics

Bone marrow: Normal female karyotype 46,XX[20].

Molecular Studies

Bone marrow:

NGS: A lymphoid NGS panel is negative for pathogenic variants. For genes assayed, see the associated PowerPoint.

Clonality: T-cell clonality is negative.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma with expression of T follicular helper markers

Interesting Feature(s)

- The initial pelvic mass biopsy was originally interpreted as a T-cell lymphoma with T follicular helper (TFH) immunophenotype. The biopsy specimen was limited and showed morphologic atypia with apparent loss of CD5 and CD7 (likely related to poor tissue viability), along with expression of follicular helper markers (PD-1 and BCL-6). In addition, rare enlarged B cells were identified.
- A subsequent bone marrow biopsy was performed for further evaluation and demonstrated an atypical infiltrate composed of numerous T cells with frequent scattered large B cells. The large atypical B cells were positive for CD20, PAX-5, BCL-6, and OCT-2. These findings were compatible with T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL).
- The morphologic distinction between T-cell/histiocyte-rich large B-cell lymphoma and T-cell lymphoma can be diagnostically challenging, particularly when the initial specimen is a needle biopsy or when samples are B-cell poor and T-cell rich with associated morphologic atypia.

Panel Diagnosis: Favor NLPB/HL with clonal T cells

EA4HP26-LYWS-289

B-cell lymphoma with a T-cell / histiocyte-rich pattern with hemophagocytosis in a pediatric patient

Dr. Tran B. Nguyen¹, Dr. Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

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Case Description

13-year-old male with no significant PMH who presented with a two-week history of abdominal pain and weight loss, along with pancytopenia, diffuse lymphadenopathy, and splenomegaly. CBC revealed a WBC of $1.3 \times 10^9/L$, hemoglobin of 7.7 g/dL, and PLT of $29 \times 10^9/L$. CXCL9 82,887 pg/mL (reference range ≤ 647 pg/mL), soluble IL-2R 19,154 U/mL (reference range 137-838 U/mL), Ferritin 921 ng/mL (reference range 7-91 ng/mL). CT demonstrated splenomegaly with multiple splenic masses, as well as multiple additional masses throughout the abdomen and pelvis. PET showed extensive hypermetabolic disease above and below the diaphragm, including widespread lymphadenopathy, splenic lesions, osseous involvement, and hepatic lesions. The patient underwent a left cervical lymph node excisional biopsy and BM biopsy. He met diagnostic criteria for HLH diagnosis. Following the final diagnosis, he received R-COPADM chemotherapy. At the most recent follow-up, there was no evidence of disease progression 16 months after completion of therapy.

Biopsy Fixation Details

Sections of the lymph node were fixed in formalin. The bone marrow core biopsy was fixed in acetic zinc formalin, followed by HCl-based decalcification.

Frozen Tissue Available

NA

Details of Microscopic Findings

LN: Sections show a lymph node with effaced architecture and a dense infiltrate of histiocytes, small lymphocytes, and scattered larger lymphoid cells with irregularly shaped nuclei, cleared chromatin, prominent nucleoli, and moderate amounts of pale cytoplasm. Some multinucleated larger forms are noted. Lymph node sinuses are largely preserved, and sinus histiocytosis is prominent.

BM: The bone marrow shows a dense infiltrate of histiocytes, including scattered hemophagocytic forms. Interspersed smaller lymphocytes and rare larger lymphoid cells with prominent nucleoli are also present.

Immunophenotype

LN: Large atypical cells are positive for CD20, CD79a, PAX-5, OCT-2, and MYC. CD3 stains numerous small T cells. PD-1 highlights numerous positive cells with some rosettes around large atypical cells. CD21 and CD23 show no expanded follicular dendritic cell meshworks associated with the abnormal infiltrate. EBER in situ hybridization was negative.

BM: The core biopsy shows rare, larger lymphoid cells with prominent nucleoli. The large cells are positive for CD20, CD79a, PAX-5, MUM-1, and OCT-2. CD68 and CD163 highlight numerous histiocytes, including frequent hemophagocytic forms.

Cytogenetics

BM: Normal male karyotype 46,XY[20]. FISH: Negative

Molecular Studies

BM: Heme Fusion panel: negative for oncogenic fusions.

Proposed Diagnosis

B-cell lymphoma, most compatible with T-cell/histiocyte-rich large B-cell lymphoma-like transformation of nodular lymphocyte-predominant B-cell lymphoma with a diffuse pattern (Fan pattern E) with abundant hemophagocytic histiocytes in the bone marrow.

Interesting Feature(s)

- In the absence of FDC meshworks, the case meets morphologic criteria for T-cell/histiocyte-rich large B-cell lymphoma, in the setting of diffuse disease involvement, including widespread lymphadenopathy and splenomegaly. However, the possibility of NLPHL with an extensive pattern E cannot be entirely excluded.
- Immunophenotypic features arguing against a de novo THRLBCL include well-formed PD-1–positive T-cell rosettes, focal areas demonstrating a mixture of small reactive B cells and larger malignant B cells, and a mixed T-cell milieu with relatively frequent CD57-positive T cells. Regardless of whether this represents a de novo process or progression from NLPHL, the findings support an aggressive B-cell malignancy.

Panel Diagnosis: THRLBCL

Nodal marginal zone lymphoma with an epithelioid histiocyte-rich pattern mimicking Lennert lymphoma

PhD/MD Taesung Jeon¹, PhD/MD Yeseul Kim²

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Case Description

A 54-year-old female Sjögren's patient with dry eyes/mouth symptoms for 1.5 years.. A palpable mass measuring approximately 2.3 cm was noted in the right submandibular area, along with bilateral cervical lymphadenopathy. An excisional biopsy was performed on the enlarged level Ib lymph node.

Biopsy Fixation Details

Formalin fixation (3.7% formaldehyde) for 24 hours.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

- Histopathological examination shows an enlarged lymph node with near-complete effacement of the normal architecture.
- The parenchyma showed extensive clusters of epithelioid histiocytes and occasional immunoblasts, resulting in a pattern reminiscent of Lennert lymphoma.
- A subset of the neoplastic B cells shows monocytoid morphology with pale-staining cytoplasm.

Immunophenotype

- B-cell component: CD20 positive; CD10 negative; BCL6 negative; BCL2 positive; MUM1 focal positive; CD5 focal positive; CD23 negative; Cyclin D1 negative; Ki-67 low.
- Additional findings: The kappa/lambda ratio exceeds 5:1, which is highly suggestive of a monoclonal process; CD68 positive in histiocytic aggregates; CD4 negative; CD8 negative; CD30 negative; PD-1 negative; CXCL13 negative; CD21 highlights follicular dendritic cell meshworks.
- EBV: many scattered positive cells in the background.

Cytogenetics

Not performed

Molecular Studies

- IGH gene rearrangement: positive.
- TCR-β gene rearrangement: negative.
- TCR-γ gene rearrangement: negative.

Proposed Diagnosis

Nodal marginal zone lymphoma

Interesting Feature(s)

Nodal marginal zone lymphoma with an epithelioid histiocyte-rich pattern mimicking Lennert lymphoma, occurring in the setting of Sjögren's syndrome and featuring a high load of EBV-positive cells in the background.

A prominent feature is the presence of numerous epithelioid histiocyte clusters, creating a histiocyte-rich pattern that closely mimics Lennert lymphoma (lymphoepithelioid lymphoma). These clusters are interspersed throughout the lymphoid stroma, potentially masking the underlying marginal zone morphology.

Panel Diagnosis: NMZL with EBV+ cells and granulomatous reaction

Unraveling NLP HL Fan Pattern C→E (THRLBCL-like) Progression with Abundant Epithelioid Histiocytes (Granuloma-like reaction): Diagnostic Pitfalls and Pattern-Stratified Therapy Needs

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Case Description

37yo F with α -thalassemia trait, NLP HL (unspecified "Fan" pattern: 2014 Stage IVB s/p R-CHOP $\times$ 6→CR), Grade 3 IDC (2020 s/p multimodal therapy) presented Sept 2025 for 2nd opinion on enlarging R supraclavicular mass. Prior outside evaluations: mature T-cell lymphoma → THRLBCL → indefinite for lymphoma. Jan 2026: progressive (8.2 cm; SUV 34.6; PET 11/2025); declining biopsy/treatment. All specimens (12/2024, 05/2020, 08/2014) were reviewed.

Biopsy Fixation Details

Formalin Fixed Paraffin Embedded

Frozen Tissue Available

No

Details of Microscopic Findings

2014 R axillary excisional biopsy: Partial nodular effacement by LP cells, predominantly pattern C with rare THRLBCL-like foci.

2020 R supraclavicular core biopsy: Minute core with rare large atypical cells in a background of T-cells admixed with numerous epithelioid histiocytes forming loose granulomas.

2024 R supraclavicular excisional biopsy: Rare large atypical cells in a T-cell/epithelioid histiocyte-rich background; no nodular architecture.

Immunophenotype

The large atypical cells were CD20+, PAX5+, OCT2+, CD79a+, BCL6+, MUM1+. While the 2014 biopsy showed retained CD21/CD23+ follicular dendritic meshwork, the 2020 and 2024 biopsies showed no evident follicular dendritic meshwork with focal IgD positivity.

Cytogenetics

CMA: Identical 5p15.1-q11.2/7q31.1-q32.3 cnLOH with VAF expansion (80% in 2014 → 100% in 2024)

Molecular Studies

NGS (275-gene panel) revealed six variants identical across all specimens except Tier 2 SETD2 splice donor variant.

Tier 2 CHEK2 p.Pro484Argfs:VAF 6.2%(2014)→2.2 %(2020)→2.6%(2024); Indeterminate TCR γ rearrangement; IgH - Non-clonal (FR2/FR3 only).

Proposed Diagnosis

Relapsed Nodular lymphocyte predominant Hodgkin lymphoma, progression from pattern C to pattern E (THRLBCL-like)

Interesting Feature(s)

This case exemplifies diagnostic/therapeutic challenges of NLP HL Fan C→E progression over 11 years, correlating histologic evolution (nodular→diffuse T/histiocyte-rich) with identical mutational architecture (ARID1B/KMT2A truncal 45-51% VAF, 5p/7q cnLOH 80→100%). Despite guidelines ignoring pattern-specific distinctions, GHSG/GLOW/COG data confirm CDEF variants predict advanced stage/relapse/transformation—yet no prospective pattern-stratified trials exist. The unspecified "Fan pattern" in 2014 report posed interpretive challenges at outside institutes (PTCL→THRLBCL→equivocal for lymphoma) without favoring relapse despite known NLP HL history. Non-necrotizing granuloma (2020→2024 epithelioid

histiocytes; 3-10% uncommon) is characteristic of progressive pattern C/E NLPHL—pitfall mimicking sarcoid/TB/granulomatous PTCL without original histology correlation. Although, scant B-cells precluded morphology/IHC diagnosis, but progressive mass, high SUV and identical molecular/genomic findings strongly indicate relapse with pattern E. Identical variants without any specific driver or clonal divergence challenges the transformation dogma. The finding of 100% 5p/7q cnLOH, encompassing the *POT1* locus, raises concern for a POT1-like tumor predisposition syndrome, given the patient's early-onset malignancies (NLPHL at age 26 and IDC at age 31). Although, patient declined therapy, relapsed pattern E NLPHL presents a therapeutic dilemma lacking guideline consensus. Indolent RT ± rituximab suits early-stage A/B/C but fails in advanced or relapse settings. R-CHOP targets pattern F/DLBCL transformation, but prior 7-year CR suggests emerging resistance. This case advocates pattern-stratified trials mirroring PET-IPS models, as C→E progression + granulomatous reaction reveals guideline-refractory biology demanding personalized escalation.

Panel Diagnosis: NLPB/HL, patterns C to E

EA4HP26-LYWS-300

Large B-cell Lymphoma with T-cell/Histiocyte Rich Background

Dr. Ruhi Hadwani, Dr. Mohamed Rabie, PhD/MD Amy Ku, Dr. Craig Soderquist, Dr. Bachir Alobeid

NYP-Columbia University Irving Medical Center, Department of Pathology and Cell Biology, New York, USA

Case Description

50-year-old female, presents with imaging showing extensive retroperitoneal lymphadenopathy. No other relevant clinical data is available/provide d.

Biopsy Fixation Details

Formalin fixed, paraffin embedded.

Frozen Tissue Available

Not performed

Details of Microscopic Findings

H&E-stained sections of the thin core lymph node biopsies reveal a diffuse polymorphic infiltrate of small lymphocytes, scattered plasma cells, and histiocytes with scattered large, atypical cells consistent with neoplastic LP-type cells. These large cells often display characteristic “popcorn-like” nuclear morphology, and in some areas are encircled by small lymphocytes forming rosette-like formations. Overall, the findings are consistent with a polymorphic infiltrate rich large cell lymphoma.

Immunophenotype

The large neoplastic cells show bright expression of CD20, PAX5, and OCT2, and are negative for CD30, CD15, IgD, p53, and EBV studies (LMP1 and EBER in situ hybridization). MYC and MUM1 show variable expression. The background demonstrates a marked paucity of small B cells. CD21 highlights only rare focal follicular dendritic cell (FDC) staining, with no FDC networks identified in additional sections. CD5 and PD-1 highlight a predominant background T-cell population; many forming rosettes around neoplastic cells, while CD57 stains a subset of background T cells.

Cytogenetics

Not Performed

Molecular Studies

Not Performed

Proposed Diagnosis

Large B-cell lymphoma with a T-cell rich background. Differential diagnosis is, diffuse component of an otherwise unsampled Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL), T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)–like variant/pattern E.

Interesting Feature(s)

This case highlights a significant diagnostic challenge in distinguishing nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)–like variant, from de novo THRLBCL on limited thin core biopsy material. Histologic examination shows scattered LP-type large cells with occasional rosette formation by surrounding lymphocytes within a diffuse, T-cell-rich background. The large, atypical cells are strongly positive for CD20, PAX5, and OCT2, and negative for CD30 and EBV, with variable expression of MYC and MUM1—an immunophenotypic profile compatible with both entities. The background is composed predominantly of CD5 and PD-1–positive T cells, with a marked paucity of small B cells and only minimal residual follicular dendritic cell networks, further contributing to the overlap with THRLBCL. In cases demonstrating a predominantly diffuse growth pattern resembling THRLBCL (pattern E), the identification of at least one unequivocal NLPHL nodule with preserved nodular architecture has been suggested to favor a diagnosis of NLPHL variant over de novo THRLBCL. However, such features cannot be demonstrated reliably or ruled out in the current case due to limited sampling inherent to core biopsy material. As a result, definitive subclassification remains challenging, underscoring the importance of adequate tissue sampling and careful clinicopathologic correlation when evaluating T-cell-rich large B-cell proliferations with LP-type cells.

Panel Diagnosis: NLPB/HL, pattern E

EA4HP26-LYWS-308

EBV positive Diffuse Large B cell lymphoma morphologically resembling T-cell/ histiocyte-rich large B-cell lymphoma

Dr. Pallavi Galera, Dr. Shenon Sethi, Dr. Ahmet Dogan

Memorial Sloan Kettering Cancer Center, Department of Pathology and Laboratory Medicine/ Hematopathology Service, New York, USA

Case Description

62 year old female presented with chief complaint of abdominal pain and weight loss

CT ABDOMEN & PELVIS: 8.3 cm right pelvic mass lesion. Extensive right pelvic and retroperitoneal lymphadenopathy

PET/CT SCAN: FDG avid retroperitoneal and pelvic lymphadenopathy and FDG avid focus in the left posterior T3 vertebral body. No FDG avid lymph nodes above the diaphragm

Biopsy Fixation Details

The biopsy was fixed in 10% formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Right Pelvic mass, biopsy: Sections of the needle core biopsy specimen reveal an atypical lymphoid proliferation composed of scattered large atypical cells with ovoid to slightly irregular nuclei, finely dispersed chromatin and conspicuous nucleoli admixed in a background rich in small lymphocytes and histiocytes.

Immunophenotype

The large atypical cells

Express: CD20 (variable), CD30, PAX5 (strong), BCL6, CD79a, MUM1, OCT2, BOB1, PDL-1, PDL-2, HLA1, HLA-

DR, BCL2 (small subset, weak), EBER (ISH), LMP1 (small subset)

Do not express: CD10, T cell markers, CD15, EBNA2

CD3 highlights a background rich in T cells that co-express CD2 & CD5 and are a mixture of CD4 and CD8+ T cells with a predominance of CD8+ cells. A substantial portion of background T-cells show expression of PD1

Cytogenetics

FISH studies : Negative for MYC, BCL2 and BCL6 rearrangements

Molecular Studies

NA

Proposed Diagnosis

EBV positive Diffuse Large B cell lymphoma morphologically resembling T-cell/ histiocyte-rich large B-cell lymphoma

Interesting Feature(s)

The biopsy reveals large atypical EBV positive B cells in a background rich in T cells and histiocytes resembling T-cell/ histiocyte-rich large B-cell lymphoma, the most common pattern in young patients but described in other age groups.

Tumor microenvironment in EBV+ DLBCL is not completely elucidated; however, PD-1/PD-L1 signaling has been described as a hallmark of EBV+DLBCL's immunosuppressive TME. This was also seen in our case with the neoplastic cells showing expression of PDL1 and the background T-cells (both CD4+ and CD8+) showing dim to intermediate expression of CD279 (PD1) by flow cytometry and immunohistochemistry.

A few studies have also shown a robust cytotoxic response as was seen in the current case with background T-cells showing inverted CD4:CD8 ratio.

Panel Diagnosis: EBV+ DLBCL

EA4HP26-LYWS-313

THRBCL with Markedly Atypical T-cells

Dr. Nicolas Lopez-Hisijos, Dr. Emily Mason

Vanderbilt University Medical Center, Nashville, USA

Case Description

- 41-year-old man with unintentional weight loss (>10kg) and fever
- Splenomegaly (27cm) and lymphadenopathy (retroperitoneal, axillary, and mesenteric)
- Elevated LDH (282 unit/L)
- Axillary lymph node biopsy >>>diagnosed as T-cell/histiocyte rich large B-cell lymphoma-THRBCL
- Treated with R-CHOP 6 cycles >>CR1
- One year post treatment, splenomegaly on surveillance PET
- Splenic core biopsy shows relapsed lymphoma
- Treated with RICE 2 cycles >> CR2, transplant consideration
- Elevated AST/ALT>>>>Liver Bx shows 2nd relapse
- Treated with glofitamab as bridge for CAR-T (current)

Biopsy Fixation Details

- Core biopsies (lymph node, spleen, and liver) fixed in 10% neutral buffered formalin.

Frozen Tissue Available

No

Details of Microscopic Findings-The three biopsies showed similar histologic findings

- Diffuse infiltrate of inflammatory cells, mostly histiocytes and small lymphocytes
- Immunoblastic cells (B and T cells)

- The largest cells were the neoplastic B-cells, with irregular nuclei, prominent nucleoli, and occasional bi-nucleation
- The inflammatory T-cells showed a range in size and morphology, including immunoblastic cells and larger cells with atypical nuclei, these were hard to discern from the neoplastic cells
- Flow cytometry, IHC, and molecular studies did not show evidence of a T-cell neoplasm

Immunophenotype

- The large neoplastic cells had a preserved B-cell immunophenotype (CD19, CD20, CD79a) and were negative for CD30
- The T-cells in the inflammatory background immunophenotypically normal, including the large immunoblastic forms
- EBER was negative

Cytogenetics

No

Molecular Studies

- T-cell gene rearrangement studies were performed on the lymph node and liver biopsies: they were both negative
- Clonaseq showed a clonal IGH sequence in the diagnostic biopsy (performed at an outside institution)

Proposed Diagnosis

- T-cell/histiocyte rich large B-cell lymphoma

Interesting Feature(s)

- The most interesting feature in this case of THRBCL is the atypical morphology and of the background T-cells.
- There was no definitive evidence a T-cell neoplasm, but the size and irregularity of some of the T-cells was worrisome, especially after the neoplasm relapsed post-treatment.
- The immunoblastic T-cells show partial CD30 positivity and were predominantly CD4 positive (although there was still a significant CD8+ population)
- The neoplastic cells were rare and hard to differentiate from reactive inflammatory cells

Panel Diagnosis: THRLBCL with atypical T cells

EA4HP26-LYWS-314

THRBCL with Paraneoplastic Symptoms Mimicking RA

Dr. Nicolas Lopez-Hisijos, Dr. Anna Dar

Vanderbilt University Medical Center, Nashville, USA

Case Description

- 52-year-old man with rheumatologic history
- Multifocal joint pain, low-grade fever, morning stiffness
- ANA neg; RF neg; elevated CRP; CCP neg
- Symptoms controlled with occasional steroid doses, methotrexate, and hydrochloroquine
- Two years later, symptoms somewhat improved, he developed a skin rash in upper extremities and presented to ED for high fever, CT-scan showed diffuse lymphadenopathy and splenomegaly
- Axillary lymph node was biopsied
- Treated with R-CHOP (6 cycles)
- Cycle 3 PET/CT scan showed excellent response
- Rash and joint pains also improved
- Currently on Cycle 5

Biopsy Fixation Details

- Axillary lymph node core biopsy
- Fixed in neutral buffered 10% formalin and embedded in paraffin (FFPE)

Frozen Tissue Available

No

Details of Microscopic Findings

- The core biopsy showed mostly histiocytes and small lymphocytes
- Complete absence of normal lymph node architecture
- Rare large cells with pleomorphic nuclei and prominent nucleoli were present
- Immunohistochemical stains were used to narrow the differential
- Again, most of the cells in the tissue sample were inflammatory (histiocytes and small T-cells)
- Large cells had strong labeling with B-cell markers, showing a retained B-cell phenotype

Immunophenotype

- The immunophenotype of the large cells is the following:
- POSITIVE: CD20, PAX5, CD19, CD79a, BCL6, and CD30 (dim partial)
- NEGATIVE: CD15, EBER, CD3, MUM1 (equivocal)

Cytogenetics

No

Molecular Studies

NO

Proposed Diagnosis

T-cell/Histiocyte Rich Large B-cell Lymphoma

Interesting Feature(s)

- Although hard to prove, it is likely that the rheumatologic symptoms the patient was experiencing were at some point paraneoplastic.
- The correct diagnosis was made radiographically when the patient presented to the ED for worsening B-symptoms.
- The symptomatology overlap between neoplastic rheumatologic conditions is well known and should prompt investigation of both differentials (especially when the serologic testing is negative or equivocal, as in this case).
- The histologic features of this case were not particularly challenging.
- CD30 was the only challenging data point to interpret: dim partial labeling of the neoplastic cells was difficult to interpret as such in the presence of immunoblastic cells with much stronger labeling (likely immunoblastic T-cells).

Panel Diagnosis: THRLBCL in setting of Rheumatoid arthritis

EA4HP26-LYWS-318

A case of Epstein-Barr virus positive diffuse large B-cell lymphoma

Dr. Raymond Yu Oo^{1,2}, **Dr. Karen Ka-Wan Yuen**²

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Case Description

58/M Chinese, immunocompetent, with underlying hypertension and diabetes mellitus, was noted to have generalized lymphadenopathy. PET/CT also showed hypermetabolic foci in lungs, liver and bone. Incisional biopsy of a neck level II lymph node was sent fresh for histopathological assessment.

Biopsy Fixation Details

The incisional biopsy was sent fresh, parts of which were fixed under 10% neutral buffered formalin for six hours.

Frozen Tissue Available

Parts of the incisional biopsy were kept frozen.

Details of Microscopic Findings

The lymph node shows extensive coagulative necrosis with sheets of atypical lymphoid cells among the background inflammatory milieu. The large-sized atypical lymphoid cells demonstrate variable morphologies, some of which feature enlarged vesicular nuclei with prominent nucleoli, some demonstrate binucleation, and some resemble mummified cells. The background inflammatory milieu is rich in small lymphocytes, histiocytes and plasma cells.

Immunophenotype

The atypical lymphoid cells are positive for CD45 and B-cell lineage markers PAX-5, CD19, CD20 and CD79a. They are also positive for EBER, CD30, CD15, BCL2, MUM1 and PDL1, and negative for CD3, CD10, cyclinD1 and ALK. Bcl-6 is <30% positive. C-Myc is not overexpressed. CD3 and CD68 highlight the background small lymphocytes and histiocytes respectively.

Cytogenetics

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Molecular Studies

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Proposed Diagnosis

Epstein-Barr virus positive diffuse large B-cell lymphoma

Interesting Feature(s)

This is a typical case of Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL). Clinically, the patient is an immunocompetent east asian at his 50s presented with generalized lymphadenopathy. Pathologically, the lymphoma is a polymorphic EBV+ DLBCL with immunoblasts and HRS-like cells among a reactive background of small lymphocytes, plasma cells, and histiocytes. The immunophenotype of the lymphoma is of the ACB/non-GCB type with CD30 and CD15 expression and diffuse PDL1 expression.

Geographic necrosis is a well-known feature of EBV+ DLBCL, as displayed in this case. It poses challenges in reaching the correct diagnosis in various aspects. Radiologically, it has been reported that the necrotic lymphadenopathy in EBV+ DLBCL mimics the necrotic pattern in tuberculosis, leading to incorrect initial diagnosis (DOI: 10.1093/qjmed/hcad084). Pathologically, extensive necrosis amplifies the possibility of sampling non-diagnostic areas and impairing the interpretation of immunohistochemical stains. A recent case series also stated that 75% EBV+ DLBCL in the series were missed by flow cytometry owing to necrosis (DOI: 10.1111/ijlh.14158). The awareness of this rare entity in necrotic specimens is, hence, of paramount importance.

EBV+ DLBCL is known to have a broad range of differential diagnoses. Differentiating it from lymphocyte-depleted classical Hodgkin lymphoma is particularly challenging, as both entities demonstrate a prominent inflammatory background and abundant HRS-like cells. The key difference lies in the immunohistochemical staining, in which lymphocyte-depleted classical Hodgkin lymphoma is typically CD45 and CD20 negative, whereas EBV+ DLBCL is CD45 and CD20 positive. Notably, the conventional diagnostic markers for lymphocyte-depleted classical Hodgkin lymphoma (CD30 and CD15) and EBER in-situ hybridization have a limited role in differentiating the two entities.

Panel Diagnosis: EBV+ DLBCL

Histiocytic-rich EBV-positive B-cell neoplasm in a limited gastric biopsy

Dr. Vrinda Shenoy², Dr. Matan Kadosh², Dr. Shafinaz Hussein¹, Dr. Amy Duffield¹, Dr. Bruce E. Petersen¹

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Case Description

A 61-year-old female with cytopenias >20 years was diagnosed with aplastic anemia (2017). Pre-transplant NGS showed *NTRK1* D109G (~51% VAF; possible germline). She underwent multiple therapies and allogeneic HSCT (Nov 2024). Pre-HSCT marrow (Jul 2024) was mildly hypocellular (~35%) with markedly decreased megakaryocytes, preserved maturation, no increased blasts/fibrosis, and no abnormal population by flow. In Jan 2025, she developed epigastric pain.

Labs: Hb 9.5 g/dL, Hct 29.5%, WBC $11 \times 10^3/\mu\text{L}$ (Lymphocytes 63%), Plt $59 \times 10^3/\mu\text{L}$, LDH 442 U/L. Plasma EBV PCR 6300 IU/mL. SPEP: no monoclonal spike. SIFE: initially faint IgA- λ band, then IgA 750 mg/dL with IgA monoclonal protein. Free light chains: λ 48.8 mg/L (κ/λ 0.35), then κ 21.7 mg/L and λ 42.8 mg/L (κ/λ 0.51). Post-HSCT chimerism: 100% donor DNA (CD3+, CD33+).

Endoscopy/Imaging: Upper endoscopy showed multiple cratered gastric ulcers (≤ 10 mm) with diffuse erythema. PET/CT: diffuse gastric FDG uptake ($\text{SUV}_{\text{max}} \leq 3.3$) without mass/adenopathy; spleen 14.8 cm without abnormal uptake.

Biopsy Fixation Details

Formalin fixed paraffin embedded.

Frozen Tissue Available

None available.

Details of Microscopic Findings

Gastric mucosa with dense polymorphous atypical lymphoplasmacytic infiltrate and focal necrosis; large atypical B cells in background of abundant histiocytes, plasma cells, and small T cells.

Immunophenotype

Neoplastic B-cells: **CD20+**, **PAX5+**, **CD79a+**, **MUM1+**, **CD30+**, **EBER+**; **CD10–**, **BCL6–**, **MYC–**, **HHV8–**, **CMV–**. Microenvironment: CD3+ T cells, CD68+/CD163+ histiocytes, CD138+ plasma cells; **Ki-67 ~70%**. Plasma cells show **λ restriction** by IHC.

Cytogenetics

Bone marrow cytogenetics showed 46,XY donor karyotype in 100% of cells, without clonal rearrangements. Interphase FISH showed disomy (normal copy number) for D8Z2 and MYC (8q24.21).

Molecular Studies

NGS: no pathogenic mutations detected; TCR and IGH/IGK rearrangements not performed.

VUS table:

Pre-HSCT (July 2024): *NTRK1* D109G (missense) 52.3%.

Post-HSCT (Jan 2025): *IRF4* splice donor c.403+2T>C 47.0%; *PLCG1* V106M 54.7%; *SAMD9* C283Y 20.0%; *SH2B3* R175W 50.4%; *STK11* I356M 49.9%.

Proposed Diagnosis

Differential diagnosis includes EBV-positive mucocutaneous ulcer (EBVMCU) versus polymorphic PTLD, EBV+, post-HSCT.

Distinction may be difficult on small/superficial biopsies. The clinical presentation of shallow circumscribed ulcers without a mass lesion or lymphadenopathy favors EBVMCU over EBV+ DLBCL [PMID: 31257347, 29615296].

Interesting Feature(s)

- This case suggests EBVMCU may present with multiple ulcers rather than a single lesion. EBVMCU classically involves oropharynx, skin, or colon [PMID: 32561847], and isolated gastric involvement is exceedingly rare [PMID: 32695342].
- The lesion microenvironment is notable for abundant histiocytes, small T lymphocytes, and clonal plasma cells (IHC lambda restriction). The concurrent clonal plasma-cell proliferation in the lesion and marrow raises the question of clonal relatedness versus a reactive process; a reactive systemic clonal plasma-cell expansion is favored based on lack of plasma-cell immunophenotypic abnormalities, absence of monoclonal spike on SPEP, and dynamic of serum free light chain studies.
- The clinical significance of IRF4 (splice), *PLCG1* V106M, *SH2B3* R175W, and *STK11* I356M is uncertain; VAFs near 50% are compatible with donor germline variants, with interpretation limited by post-transplant context.

Panel Diagnosis: EBV+ PTLD

EA4HP26-LYWS-322

T-cell/histiocyte-rich large B-cell lymphoma of epidural soft tissue developing in a treated diffuse large B-cell lymphoma

Dr. Vrinda Shenoy, Dr. Matan Kadosh, Dr. Abdelsalam Sharabi

Icahn School of Medicine at Mount Sinai, Department of Pathology, Molecular & Cell-Based Medicine, Mount Sinai West, New York, USA

Case Description

A 37-year-old male with a history of stage IV diffuse large B-cell lymphoma (DLBCL), activated B-cell (ABC) subtype, diagnosed in 2019 with involvement of retroperitoneal and axillary lymph nodes, pleura, spleen, and skin and treated with R-DA-EPOCH and R-CHOP, with high-dose methotrexate for CNS prophylaxis. Prior FISH demonstrated trisomy 3, trisomy/tetrasomy 8, trisomy 14, and trisomy 18, with no *MYC*, *BCL2*, or *BCL6* rearrangements. In March 2025, he presented with upper back pain and right arm paresthesias. Imaging demonstrated a paravertebral mass with epidural extension and disseminated FDG-avid nodal and extranodal disease. An excisional biopsy of a right cervical lymph node was performed.

Laboratory Findings:

CBC: Hb 15.1 g/dL, Hct 46%, WBC $12.3 \times 10^3/\mu\text{L}$, platelets $294 \times 10^3/\mu\text{L}$. Albumin 5.0 g/dL. LDH 191 U/L.

Endoscopy / Imaging:

CT cervical spine: 7.0 cm paravertebral mass abutting the right lung apex with extension into the right C7–T3 neural foramina and spinal canal.

PET/CT: diffuse FDG uptake (SUVmax 21.5) involving intrathoracic and portacaval lymph nodes, spleen, bones, and the paravertebral mass.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

There is diffuse, vaguely nodular effacement of the tissue architecture. At low magnification, the involved tissue has a characteristic pale eosinophilic appearance attributable to the background histiocytic population that is also mixed with increased small lymphocytes. The neoplastic large cells are randomly scattered, without formation of aggregates or sheets.

Immunophenotype

Neoplastic B-cells: CD20+, PAX5+, OCT2+, MUM1+, BCL2+, BCL6+, CD30+, with increased Ki-67 proliferative index, CD10-, CD15-, ALK-, c-MYC-, EBER-, IgD-.

Microenvironment: abundant CD3+ small T-cells and CD68+ histiocytes; PDL-1 shows nonspecific weak staining; CD21 highlights absence of follicular dendritic cell network (FDC).

Cytogenetics

Not performed.

Molecular Studies

T-cell receptor rearrangement studies (TCR β and TCR γ): no discrete clonal rearrangements detected, consistent with a polyclonal T-cell population.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL).

Interesting Feature(s)

TCHRLBCL accounts for <10% of large B-cell lymphomas, presenting predominantly with infradiaphragmatic lymph node involvement. Our patient presented with Lugano stage IV disease, having splenic and extranodal (spinal epidural) soft tissue and bony involvement.

Spinal involvement of TCHRLBCL at presentation is exceedingly rare; it has been described in case reports and rare case series. (PMID: 9813978, 12409722).

Sequential emergence of de novo TCHRLBCL in a patient with treated ABC-subtype DLBCL is a unique scenario and raises important diagnostic considerations in the post-therapy setting.

Post-treatment large B-cell lymphomas may exhibit therapy-related immune remodeling (T-cell/histiocyte enrichment, B-cell depletion, stromal changes), producing a pattern that can mimic TCHRLBCL. (PMID: 27895166) Our case displays a diffuse and uniform distribution of neoplastic B-cells forming <10% of cellularity, with a monotonous tumor microenvironment rich in small T-cells and histiocytes with no residual follicular architecture. No histologic evidence of therapy effect (e.g., scarring/fibrosis, necrosis, foamy macrophages) are identified. Taken together, these findings best support a diagnosis of TCHRLBCL rather than therapy-modified recurrent DLBCL.

Panel Diagnosis: THRLBCL

EA4HP26-LYWS-324

When Histiocytes Hide the Lymphoma: A Granulomatous Variant of High-Grade Follicular Lymphoma

Dr. Barina Aqil

Northwestern University, Pathology, Chicago, USA

Case Description

A 59-year-old female presented with inguinal lymphadenopathy. PET/CT showed diffuse lymphadenopathy (highest SUV was 31). Initial laboratory studies were remarkable for anemia, leukocytosis, absolute neutrophilia, elevated LDH (438 units/L) and C-reactive protein (229.6 mg/dl).

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Inguinal lymph node biopsy was performed, which showed cylindrical cores of fibroadipose and lymphoid tissue with an atypical diffuse to vaguely nodular lymphoid infiltrate admixed with increased histiocytes (forming ill-defined

granulomas) and small lymphocytes. The infiltrate consisted of large cells with irregular nuclear contour, vesicular chromatin and prominent nucleoli. Numerous apoptotic bodies were seen.

Immunophenotype

The atypical lymphoid infiltrate was positive for CD20, PAX5, CD10 (variable, subset), BCL6 (subset), MUM1 (variable >30%), BCL2 (weak, >50%), c-MYC (~10%), and negative for CD5 and EBER. CD23 and CD21 showed expanded follicular dendritic cell meshworks. Ki-67 revealed high proliferative index (~70%). Flow cytometry showed a kappa light chain restricted monotypic B-cell population that was dim CD19+, CD20+, dim CD10+ and CD5-. The admixed histiocytes showed no abnormal antigen expression and special stains (AFB, GMS) were negative.

Cytogenetics

FISH was negative for *IRF4* gene rearrangement. FISH analyses (*BCL2*, *BCL6*, and *MYC* gene rearrangements) are pending.

Molecular Studies

Next generation sequencing also is pending.

Proposed Diagnosis

At least follicular lymphoma, histologic grade 3B (FL3B)/follicular large B-cell lymphoma (FL-LBCL).

Interesting Feature(s)

This case illustrates how FL3B/FL-LBCL can present with prominent histiocytes and ill-defined granulomas, creating a diagnostic pitfall that mimics reactive or infectious processes. The immunophenotype highlights the biologic heterogeneity of FL3B, which often shows mixed germinal-center and post-germinal-center markers, blurring the boundary between follicular lymphoma and diffuse large B-cell lymphoma (DLBCL). Presence of follicular dendritic cell meshworks support a FL rather than DLBCL. The increased histiocytes are particularly interesting as literature has reported that FL3B and other ABCs may show histiocyte-rich or granulomatous variants, which can obscure neoplastic cells and delay diagnosis. These cases must be distinguished from histiocyte-rich DLBCL, T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), and infectious granulomatous lymphadenitis, emphasizing the importance of immunophenotyping and FDC meshwork assessment. The high SUV (31) on PET/CT and elevated inflammatory markers (CRP, LDH, neutrophilia) align with the aggressive biology of FL3B, which behaves more like DLBCL than low-grade FL. Pending FISH and NGS studies are clinically meaningful because FL3B may lack the classic *BCL2* rearrangement of low-grade FL and instead show *BCL6* or *MYC* alterations, or mutations in genes associated with transformation and high-grade behavior.

Overall, this case underscores that FL3B is a biologically and morphologically distinct entity, capable of presenting with granulomatous/histiocyte-rich patterns, attenuated germinal-center markers, and aggressive clinical features. Recognizing these atypical presentations is essential to avoid misdiagnosis and ensure appropriate staging and therapy.

Panel Diagnosis: FL grade 3, histiocyte rich background

EA4HP26-LYWS-325

EBV-associated transformation of follicular lymphoma

Dr. Parastou Tizro, Dr. Olga Danilova, Dr. Young Kim, Dr. Raju Pillai, Dr. Winston Lee, Prof. Lorinda Soma, Prof. Joo Song, Prof. Michelle Afkhami, Prof. Karl Gaal

City of Hope Medical Center, Pathology, Duarte, USA

Case Description

A 65-year-old immunocompetent man presented with progressive abdominal discomfort and distension. Imaging demonstrated a left ureteral mass causing obstruction with hydronephrosis and generalized FDG-avid lymphadenopathy (SUV max up to 17.6), prompting excisional biopsy of a right axillary lymph node.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

NA

Details of Microscopic Findings

The lymph node shows striking histologic heterogeneity.

- In some areas, it is composed of closely packed abnormal follicles with attenuated mantle zones, populated predominantly by centrocytes with increased centroblasts (>15/HPF).
- In contrast, separate nodular and partially sclerotic areas show a polymorphous inflammatory background rich in histiocytes and small lymphocytes, with rare scattered eosinophils and plasma cells, admixed with focally clustered large atypical Hodgkin-like cells containing prominent macronucleoli.

Immunophenotype

Immunohistochemistry stains:

- **Follicular component:**
- Positive: CD20, PAX5, CD10, BCL6, MEF2B, BCL2, CD21 (preserved FDC's meshwork's), MUM1 (subset), Ki-67 40-70%, EBER (rare scattered cells/possibly transition zones)
- Negative: CD3, CD30 (predominantly negative)
- Tumor microenvironment: CD4/PD1 (numerous TFH cells; intrafollicular), CD8 (relatively less; interfollicular), ICOS (similar to PD1)
- **Areas containing large/Hodgkin-like cells:**
- Large cells:
- Positive: CD20 (uniform), CD19, CD30 (heterogenous), CD45 (mostly), PAX5 (moderate), OCT2, BOB1, CD79a, BCL6 (weak), MEF2B, BCL2, MUM1, EBER, TARC (subset), Ki-67 >90%
- Negative: CD3, CD10 (predominantly negative), CD15, CD21 (no meshwork)
- Tumor microenvironment: CD8/TIA1 (markedly increased cytotoxic T-cells), PD1 (strong, diffuse), PDL1 (macrophages and subset of tumor cells), CD68, CD163 (increased number)

Flow cytometry:

- Positive: CD19 (slightly decreased), CD20, CD10, CD38 (dim), BAFF-R
- Negative: CD5, CD11c, CD23, CD25, CD103, CD200

Cytogenetics

FISH (BCL2 break apart), pending

Molecular Studies

NGS on both components is in progress

Proposed Diagnosis

Follicular lymphoma (FL), grade-3A with focal transformation to EBV+ CD30+ large B-cell lymphoma

Interesting Feature(s)

- Rare example of "EBV-associated transformation of FL", in an immunocompetent patient
- Composite/divergent morphology with coexistence of conventional FL and large B-cell lymphoma with Hodgkin-like features
- Hodgkin-like morphology, but retention of a B-cell program in EBV+ large cells, supporting EBV-positive large B-cell lymphoma
- Marked tumor microenvironment reprogramming, shifting from a TFH-rich follicular niche in FL areas to a CD8-predominant, macrophage-rich, PD-1/PD-L1-positive inflammatory milieu in the large cell areas
- EBV positivity associated with immune checkpoint activation and microenvironmental evolution

1. Tsuyuki U, et al. Follicular lymphoma with EBV-associated transformation: A case report and review of literature: J Exp Hem 2024; 64(2);144-148
2. Granai M, et al. Role of Epstein-Barr virus in transformation of follicular lymphoma to diffuse large B-cell lymphoma: a case report and review of the literature. *Haematologica*. 2019;104(6):e269-e273.

3. Sarkozy C, et al. Integrated single cell analysis reveals co-evolution of malignant B cells and tumor micro-environment in transformed follicular lymphoma. *Cancer Cell*. 2024;42(9):1630.

Panel Diagnosis: FL grade 3, transformation to EBV+ CD30 LBCL

EA4HP26-LYWS-326

EBV-associated Burkitt lymphoma with prominent granulomatous reaction

Biljana Grcar Kuzmanov¹, Gorana Gasljevic^{2,1}, Dora Panna¹

¹ Institute of Oncology Ljubljana, Ljubljana, Slovenia; ² Medical faculty Maribor, Maribor, Slovenia

Case Description

24-yrs-old male patient, otherwise healthy. In October 2023, he has noticed enlarged lymph node in left axilla. Laboratory results at admission: L 8.23×10^9 , Hgb 154 g/L, Plt 281×10^9 , LDH 283 ukat/L (normal <4.13), CRP 8.2 mg/L (normal <5). Serology for HIV, HCV negative, anti HBs reactive 95 IE/L (post vaccination), anti HBc, anti HBcIgM, antiHBe and anti HBsAg all negative. PET CT: increased uptake in left axilla with SUV 28.8, without other hypermetabolic foci elsewhere in the body. Bone marrow biopsy and aspirate negative. Cerebrospinal fluid negative for lymphoma cells. IPI 0. Clinical stage IA. Treated according BFM protocol with intratechal metotrexate until December 2023. Complete remission. Last control June 2025, asymptomatic, in complete remission.

Biopsy Fixation Details

10% buffered formalin overnight.

Frozen Tissue Available

Yes

Details of Microscopic Findings

Diffuse, cohesive proliferation of monomorphic medium-sized lymphoid cells with basophilic cytoplasm, squared-off cytoplasmic borders, round nuclei with finely clumped and dispersed chromatin, and multiple basophilic and paracentrally located nucleoli. Abundant mitoses and apoptosis with many tingible body macrophages and starry sky pattern. Besides, a florid granulomatous reaction is present.

Immunophenotype

CD20+, CD10+, BCL6+, c-myc 100%+, EBV ISH +; BCL2-, CD3-, TdT-, EBNA2-, EBV-LMP-; MIB-1 100%

Cytogenetics

MYC translocation by FISH. No BCL2 and BCL6 translocations.

Molecular Studies

NA

Proposed Diagnosis

WHO HEAEM5: EBV-associated Burkitt lymphoma with prominent granulomatous reaction.

ICC2022: Sporadic EBV-associated Burkitt lymphoma with prominent granulomatous reaction.

Interesting Feature(s)

Rare cases of EBV-associated Burkitt lymphoma show a florid granulomatous reaction and are characterised by a favourable outcome and, in rare instances, spontaneous regression. They are characterized by a proinflammatory microenvironment, typically present with limited-stage disease, and have an especially good prognosis. BL in the setting of a granulomatous reaction and conspicuous monocytoid B-cell hyperplasia might be easily overlooked; establishing the correct diagnosis may be challenging.

Panel Diagnosis: BL with granulomatous reaction

“Complex Cytogenetic Aggressive B-Cell Lymphoma Confined to Bone Marrow Presenting as HLH-Like Syndrome”

Prof. Samah Kohla^{1,2}, Dr. Aliaa Amer¹, Dr. Sarah ELKourashy^{3,2}, Dr. Amna Gameil^{3,2}, Dr. Amal Aly⁴, Dr. Samah Kohla performed and interpreted the bone marrow examinations, prepared the abstract, and submitted the case. Dr. Aliaa Amer reviewed the bone marrow. Dr. Sarah ELKourashy managed the clinical care of the patient. Dr. Amna Gameil reviewed the abstract. Dr. Amal Salm reported the cytogenetic studies.

¹ Hamad Medical corporation, DLMP, Hematology Division/NCCCR, Doha, Qatar; ² Weill Cornell Medicine-Qatar, Clinical pathology Department, Clinical pathology Department, Doha, Qatar; ³ Hamad Medical Corporation, NCCCR, Clinical Hematology Department, Doha, Qatar; ⁴ Hamad Medical corporation, Cytogenetic and Molecular Genetic Division, Doha, Qatar

Case Description

A 48-year-old woman with seropositive rheumatoid arthritis, hypothyroidism, and secondary fibromyalgia presented with fever, abdominal & chest pain, and shortness of breath. Laboratory evaluation revealed bicytopenia with a leukoerythroblastic picture and circulating atypical lymphoid cells. Viral screen was positive for human rhino/enterovirus. CT imaging showed hepatosplenomegaly. She developed metabolic acidosis, hyperlactatemia, and tachycardia, requiring MICU admission for presumed septic shock. Hematology consultation and bone marrow evaluation were undertaken given concern for secondary hemophagocytic lymphohistiocytosis (HLH).

Biopsy Fixation Details

Bone marrow aspirate smears and clot sections; fixation details not specified.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

P.B smear revealed hypochromic microcytic anemia with nucleated red cells, dysgranulopoiesis, monocytosis, lymphocytosis, and ~14% atypical lymphoid cells. Bone marrow aspirate was particulate and hypercellular with numerous degenerated cells; large atypical lymphoid cells morphologically similar to those in peripheral blood were present. Megakaryocytes were markedly decreased. Prominent histiocytic proliferation with hemophagocytosis was noted. Clot sections demonstrated near-total marrow replacement by medium to large abnormal lymphoid cells with irregular nuclear contours, open chromatin, and prominent nucleoli, with marked suppression of trilineage hematopoiesis. By IHC the neoplastic cells were diffusely positive for CD20, PAX5, CD79a, and BCL2, and negative for CD10, CD5, BCL6, CD23, CD43, and Cyclin D1. Background T-cells were highlighted by CD3. CD68 and CD163 highlighted markedly increased histiocytes with hemophagocytosis. MPO, glycophorin A/E-cadherin, and VWF/CD61 confirmed suppression of granulopoiesis, erythropoiesis, and megakaryopoiesis

Immunophenotype

Flow cytometry on P.B shows 8% B-cells express CD19, CD20, CD79b, IgM, IgD and cBcl2 with partial CD38, CD200, CD43 and CD23 and include a subpopulation (4%) with higher light side scatter and expressing dim CD10, and appears monotypic with dim cytoplasmic kappa light chain restriction. Flow cytometric analysis of BM aspirate identifies (1%) monotypic B-cell population with kappa light chain restriction. Additionally, a small aberrant T-cell population (~1%) is noted.

Cytogenetics

iFISH revealed extra copies of IGH and BCL6 rearrangement (~40% of cells). Karyotype showed a complex abnormal clone: 45,X,-

X,t(1;6)(p34;q21),t(1;17)(p36.1;q11.2),add(3)(q11.2),der(6)add(6)(p25)add(6)(q21),add(8)(p21),?t(8;14)(p21;q32),add(10)(q26)[15]/46,XX[5].

Molecular Studies

N/A

Proposed Diagnosis

P.B and BM findings are consistent with aggressive B-cell lymphoma with extensive marrow involvement. Prominent hemophagocytosis raises the possibility of secondary HLH, potentially triggered by underlying infection, medication, or malignancy.

Interesting Feature(s)

This case illustrates unusual aggressive B-cell lymphoma with predominant bone marrow involvement, prominent hemophagocytosis, and clinical presentation mimicking secondary HLH and septic shock. Minimal detectable disease by flow cytometry despite extensive marrow infiltration highlights diagnostic challenges. Complex cytogenetic abnormalities, including IGH gain and BCL6 rearrangement, further underscore the rarity and clinical significance. This case emphasizes the importance of integrating clinical, morphologic, immunophenotypic, flow cytometric, and cytogenetic findings for accurate diagnosis and management.

Panel Diagnosis: DLBCL, with prominent hemophagocytosis, setting of RA

EA4HP26-LYWS-359

EBV-positive large B cell proliferation in a TFH-rich background

Dr. Ingrid Tam, Dr. Ali Sakhdari

University Health Network, University of Toronto, Laboratory Medicine and Pathobiology, Toronto, Canada

Case Description

- 86F presenting to the hospital with 5 days of weakness, poor appetite, and progressive fatigue
- Found to be significantly hypercalcemic (3.91 mmol/L on presentation)
- CT:
 - Multiple enlarged retroperitoneal, abdominal, and mediastinal lymph nodes
 - Splenomegaly (15.4 cm)
- Neck ultrasound:
 - Enlarged, palpable lymph nodes in left Level 1B and 2A
 - An open biopsy of the left cervical lymph node (level 2A) was performed

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Architecture is effaced by a lymphohistiocytic infiltrate.

Scattered large, pleomorphic cells with immunoblastic and Hodgkin-like morphology

Immunophenotype

- Large immunoblastic/Hodgkin-like cells:
 - Positive for CD20, PAX5, MUM1 (strong), OCT2, BCL6 (rare, variable), CD30 (rare), and EBER ISH
 - Negative for CD10 and CD15
 - Ki-67 proliferation index of ~60%
- T-cells:
 - Mostly CD4+ type
 - Intact pan-T-cell antigen expression (CD2, CD5, CD7)

Positive for PD1 (variable) and BCL6 (variable, weak)

Negative for CD10, ICOS, and EBER ISH

- Flow cytometry demonstrated:

Polytypic B cells T cells that were predominantly CD4-positive with intact pan-T-cell antigen expression and polyphasic TCRBC1 expression

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

EBV-positive diffuse large B-cell lymphoma, pleomorphic variant

Interesting Feature(s)

- Morphologic and immunophenotypic overlap with classic Hodgkin lymphoma:
 - Hodgkin-like/Reed-Sternberg-like cells in a mixed inflammatory milieu
 - Large cells with strong MUM1 expression, positivity for MUM1 (strong) and EBER ISH
- TFH-rich microenvironment as a diagnostic pitfall
 - Abundant background T cells with expression of TFH markers
- Resolution by integrated assessment of immunophenotype
 - EBV distribution: EBER ISH positive in small and large cells
 - Preservation of the B-cell transcriptional program: positive for CD20, PAX5, OCT2

Panel Diagnosis: EBV+ DLBCL

EA4HP26-LYWS-361

Nodular Lymphocyte Predominant Hodgkin Lymphoma, pattern E with secondary EBV infection

Dr. Ingrid Tam, **Dr. Ali Sakhdari**

University Health Network, University of Toronto, Laboratory Medicine and Pathobiology, Toronto, Canada

Case Description

- 30M presenting to the hospital with a month-long history of fevers and lethargy
- History of neurofibromatosis type 1, asthma, hypothyroidism
- CT:
 - Bilateral lower neck adenopathy involving levels 4, right level 5B, lower paratracheal regions, supraclavicular fossa
 - Mediastinal adenopathy
- Biopsy of the left supraclavicular lymph node was performed

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Architecture is effaced by a vaguely nodular to lymphohistiocytic infiltrate.

Large cells with multilobulated clear nuclei and eosinophilic cytoplasm are scattered throughout.

Large cells show irregular, densely eosinophilic nuclei, variably prominent nucleoli, and moderate cytoplasm.

Immunophenotype

- Large "popcorn" cells:
 - Positive for CD20, PAX5, CD19 (weak), MUM1 (variable), CD15 (subset, weak), OCT2
 - Negative for CD30, EBER ISH
- Scattered larger cells:
 - Positive for CD30 and EBER ISH
- Flow cytometry showed: Polytypic B cells
 - Predominance of T cells (91% of all lymphocytes) with a CD4/CD8 ratio of 7.3

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Nodular lymphocyte predominant Hodgkin lymphoma, pattern E

Interesting Feature(s)

- Coexistence of classic LP ("popcorn") cells and Hodgkin-Reed-Sternberg-like large cells within the same lesion, creating morphologic overlap with classic Hodgkin lymphoma
- Immunophenotypic separation between neoplastic LP cells (CD20+, PAX5+, OCT2+, CD30-, EBER-) and background activated/EBV-positive immunoblasts (CD30+, EBER+) allowed classification as NLPHL, pattern E

Panel Diagnosis: NLPB/HL, pattern E

EA4HP26-LYWS-363

Composite Lymphoma of EBV-Positive Diffuse and Follicular Large B-cell Lymphoma and Mantle Cell Lymphoma with Increased Epithelioid Histiocytes

Dr. You-Wen Qian, Dr. Maurice Barcos

Roswell Park Comprehensive Cancer Center, Department of Pathology, Buffalo, USA

Case Description

The patient is a 66-year-old man who was admitted to an outside hospital on 9/15/2025 with acute altered mental status and fever. His medical history includes hypertension, type 2 diabetes mellitus with stage 3 chronic kidney disease, obesity, coronary artery disease, chronic pain, COPD, GERD, prior DVT/PE on chronic anticoagulation, and hyperlipidemia. On presentation, he was febrile to 104.5°F, tachycardic, and encephalopathic. CT imaging of the abdomen and pelvis demonstrated diffuse lymphadenopathy. Cerebrospinal fluid analysis showed elevated protein; an extensive infectious workup, including cultures, HSV/VZV PCR, and cryptococcal antigen testing, was negative. An axillary lymph node excisional biopsy was performed. The patient was transferred to our institution on 10/13/2025 for further care, and the pathology slides were submitted for review. Following confirmation of the diagnosis, he received six cycles of R-CHOP therapy.

Biopsy Fixation Details

The lymph node was formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin.

Frozen Tissue Available

NA

Details of Microscopic Findings

The lymph node architecture is largely effaced by a heterogeneous lymphoid infiltrate composed of small lymphoid cells, large atypical lymphoid cells, and increased epithelioid histiocytes, with regional variation. Small lymphoid cells expand the mantle zones. Large atypical lymphoid cells with centroblast morphology are present both within and outside nodules and are frequently associated with epithelioid histiocytes; a subset shows pleomorphic features. Calcified microgranulomas and focal necrosis are identified.

Immunophenotype

By immunohistochemistry, the large atypical lymphoid cells are positive for CD20, PAX5, CD10, CD30 (20%), EBER (>80%), MUM1, and BCL6, and negative for CD5, BCL1, BCL2, CD15, ALK1, HHV8, and pancytokeratin (AE1/3). The small lymphoid cells, predominantly in a mantle zone distribution, are positive for CD20, PAX5, BCL2, CD5, BCL1, and SOX11, and negative for CD10, BCL6, ALK1, EBER, HHV8, CD30, CD15, EMA, and pancytokeratin. CD21 and CD23 highlight partially disrupted follicular dendritic cell networks. CD138 identifies <5% polytypic plasma cells. AFB and GMS stains are negative.

Cytogenetics

FISH analysis is negative for rearrangements of MYC, CCND1, BCL2, and BCL6.

Molecular Studies

Next-generation sequencing detected KMT2D p.T300Nfs42 (8.7% VAF), IGHG3 p.G16 (7.2% VAF), and IGHG3 p.L1P (10.0% VAF). ClonoSEQ analysis identified five dominant sequences.

Proposed Diagnosis

Composite lymphoma composed of EBV-positive diffuse and follicular large B-cell lymphoma and mantle cell lymphoma with increased epithelioid histiocytes.

Interesting Feature(s)

This composite lymphoma with EBV-positive large B-cell lymphoma and mantle cell lymphoma in an unusual growth pattern is rare. The presence of both EBV-positive diffuse large B-cell lymphoma and EBV-positive follicular large B-cell lymphoma in this case suggests a potential role for EBV in disease progression. The large B-cell component expresses PD-L1 and CD30, which may offer therapeutic targets in refractory disease. The genetic mechanisms underlying this composite lymphoma remain unclear; although common rearrangements are absent, IGHG3 mutations warrant further investigation. Increased epithelial histiocytes in DLBCL have been reported previously with a favorable prognosis, but uncertain in the settings of EBV-positive diffuse large B-cell lymphoma or composite lymphoma.

Panel Diagnosis: EBV+ DLBCL and Mantle cell lymphoma with epithelioid histiocytes

EA4HP26-LYWS-366

Bridging Immune Dysregulation and Malignancy: B-Cell Lymphoma in the Context of Immunodeficiency

Dr. Bianca N. Adams, Dr. René P. Michel, Dr. Nadine Demko

McGill University Health Center, Pathology, Montréal, Canada

Case Description

A 31-year-old male chemist presented with longstanding lymphadenopathies and de novo constitutional symptoms. Since 2013, patient was known for splenomegaly and intermittent immune thrombocytopenia/neutropenia usually during infections, requiring splenectomy and multiple immunomodulatory therapies (IVIg, azathioprine, rituximab, prednisone, and pulse dexamethasone). PET CT showed diffuse enlarged supra and infra diaphragmatic lymph nodes (e.g. right axillary 3.2 cm, SUV 17.8; right inguinal 1.9 cm, SUV 14.3). Peripheral blood showed leukopenia (WBC $2.9 \times 10^9/L$) and neutropenia (ANC $0.4 \times 10^9/L$). Extensive workup ruled out immune, autoimmune, and

infectious causes. Autoimmune lymphoproliferative syndrome (ALPS) testing was negative. The patient is responding to sirolimus.

Biopsy Fixation Details

The fresh right axilla specimen was received as two samples (6.5 x 5.2 x 4.0 cm; 2.0 x 1.1 x 0.8 cm) for flow cytometry, snap freeze, B+ and formalin fixation.

Frozen Tissue Available

Yes

Details of Microscopic Findings

Histology revealed lymph nodes with a nodular pattern composed of epithelioid histiocytes, small lymphocytes with scattered medium to large atypical cells between nodules. A subset of the larger cells were lymphocyte-predominant (LP)/popcorn-like cells, showing enlarged, lobulated nuclei with variably prominent nucleoli. Fibrous bands, poorly-formed granulomas, necrosis, and eosinophils were also present.

Immunophenotype

Small nodular B-cells were CD20/CD79a/PAX5-positive. LP-like cells were positive for CD45, CD20, CD79a, PAX5, BCL6, OCT2, and BOB1; CD30 and CD15 were limited to activated and myeloid cells, respectively. Numerous background small T cells (CD2, CD3, CD5, CD7, CD4>CD8) and histiocytes (CD68) were present, with focal PD-1 rosettes around LP-like cells, rare ICOS/CXCL13-positive cells, and focally expanded CD21/CD23 follicular dendritic cell meshworks. MUM1 stained plasma cells. Ki-67 highlighted 30-40% of lymphoid cell nuclei. EBER ISH, EBV-LMP1, HHV8, CMV, spirochete stains, acid-fast, PAS and Grocott stains were negative and other markers were non-contributory.

Flow cytometry showed a reactive distribution: 94% lymphocytes, including 73% T-cells (CD4:CD8 of 6:1), 22% B-cells (k:l of 1.4:1), and 5% NK-cells.

Cytogenetics

Not applicable

Molecular Studies

Molecular studies showed suspicious IGH peaks in *FR1/FR2* (outside valid size range) and a small *IGK* clonal peak on core biopsy (no T-cell clonality), but no B-cell clonality on excisional biopsy and an inconclusive *TCRβ-C* finding. A Blueprint Genetics 274-gene primary immunodeficiency panel was negative for ALPS-related genes, identifying a pathogenic *RMRP* variant and VUS in *RAG1/ITK*. Additional testing, including tumor whole exome sequencing and an extended Blueprint Genetics panel, are pending.

Proposed Diagnosis

Nodular lymphocyte predominant B-cell lymphoma, grade 1 (ICC 2022)/ Nodular lymphocyte predominant Hodgkin lymphoma, Fan pattern C (WHO 5th edition)

Interesting Feature(s)

This case highlights a challenging diagnosis of NLPBL/NLPHL secondary to sparse and morphologically subtle LP cells obscured by reactive histiocytes and T-cells, with only focal rosetting and lack of definite B-cell clonality. Diagnosis in part was reached by excluding differentials including lymphocyte-rich classical Hodgkin lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, progressive transformation of germinal centers and reactive causes. The patient's medical history and VUS in immune/lymphoproliferation-related genes suggestive of immune dysregulation, influencing treatment de-escalation from RCHOP to R-CVP plus sirolimus, as was done in this case.

Panel Diagnosis: NLPB/HL

EBV+ Diffuse large B-cell lymphoma with a T-cell/histiocyte-rich background.

Dr. Ruhi Hadwani, Dr. Mohamed Rabie, PhD/MD Amy Ku, Dr. Craig Soderquist, Dr. Bachir Alobeid

NYP-Columbia University Irving Medical Center, Department of Pathology and Cell Biology, New York, USA

Case Description

A 28-year-old male patient presented with a one-week history of fatigue, nausea, and vomiting, as well as marked unintentional weight loss of approximately 70 lb. over one year. The patient is HIV negative. CT imaging of the abdomen and pelvis revealed severe pelvic and abdominal lymphadenopathy, hepatosplenomegaly, and a dominant right lower quadrant soft tissue mass. Despite treatment, the patient later experienced loss of response, with biopsy-proven disease relapse four years later.

Biopsy Fixation Details

Formalin fixed

Frozen Tissue Available

Not performed

Details of Microscopic Findings

Histologic sections from the excisional lymph node biopsy demonstrate complete effacement of the nodal architecture by a diffuse, anastomosing, serpiginous lymphohistiocytic proliferation. The infiltrate is composed predominantly of small lymphocytes and histiocytes, admixed with scattered and loosely aggregated atypical large cells with prominent eosinophilic nucleoli, reminiscent of Hodgkin/Reed–Sternberg-like cells and variants. These atypical cells are distributed in a rich inflammatory background and are associated with conspicuous geographic areas of necrosis.

Immunophenotype

Immunohistochemical and in situ hybridization studies demonstrate that the atypical large cells express B-cell-associated markers, including CD20, CD79a, PAX5, and CD22 (focal, weak), with partial, weak CD19 expression. The neoplastic cells show variable expression of BCL6, PDL1, MUM1, and subset, weak positivity for CD30, BOB1, and OCT2. The cells are positive for LMP1 and EBV-ISH, supporting EBV association, and showing focal PD-1 expression. CD21 highlights no follicular dendritic cell meshwork. The background is composed of numerous reactive T cells highlighted by CD3, with a marked CD4 predominance and occasional rosetting around neoplastic cells, and abundant admixed histiocytes highlighted by CD68.

Cytogenetics

Showed a normal karyotype with no clonal chromosomal abnormalities detected. FISH analysis using IGH and BCL6 break apart probes showed no evidence of clonal rearrangement.

Molecular Studies

Not performed

Proposed Diagnosis

EBV-positive Diffuse large B-cell lymphoma NOS with T-cell/histiocyte-rich background.

Interesting Feature(s)

EBV-positive diffuse large B-cell lymphoma (DLBCL), NOS, typically occurs in older adults due to defective immune surveillance associated with immunosenescence and is uncommon in young, immunocompetent patients. This case in a 28-year-old shows an unusual T-cell/histiocyte-rich (THR-like) microenvironment that can mimic THRLBCL or NLPHL-like patterns. EBV detection by LMP1 and EBV-ISH confirms a pathogenetically distinct process. The THR-like morphology reflects EBV-driven immune modulation, latent LMP1 expression activates NF-κB and JAK/STAT signaling, inducing cytokines and chemokines that recruit T cells and histiocytes, while upregulating immune checkpoints, including PD-1/PD-L1 and IDO, leading to T-cell exhaustion and ineffective anti-tumor immunity. Unlike EBV+ DLBCL in older adults, where impaired immune surveillance drives tumor growth, young

patients typically retain immunocompetence, exhibit latency II EBV, and often have favorable clinical outcomes despite aggressive histologic features, highlighting the age-dependent differences in pathogenesis and the critical role of the immune microenvironment.

Panel Diagnosis: EBV+ DLBCL

EA4HP26-LYWS-378

EBV-positive Large B-cell lymphoma incidentally identified in an amputated specimen

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Case Description

36-year-old male involved in a motor vehicle collision and initially managed conservatively for pain control. He subsequently re-presented with compartment syndrome and a phlegmon consistent with thoracic outlet syndrome. Despite serial fasciotomies and wound debridements during the admission, the clinical course progressed, ultimately necessitating left arm above-elbow amputation. The amputated limb was submitted for pathological evaluation.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

No

Details of Microscopic Findings

- Sections show a diffuse proliferation of atypical lymphoid cells infiltrating dermis, subcutaneous adipose tissue, skeletal muscle and focally large blood vessels, sparing the epidermis.
- The atypical cells are intermediate in size, monomorphic, with scant cytoplasm, round to mildly irregular nuclear contours, finely granular chromatin and multiple small nucleoli. Mitotic activity is brisk, and apoptotic cells and scattered admixed tingible-body macrophages are present imparting a "starry sky" appearance.
- Focal arterial occlusion is noted, with recanalization of the vascular lumen; rare thrombosed small blood vessels are also present.
- Patchy tumor necrosis and soft tissue necrosis is present, and dermal necrosis is noted in specimen
- The skin at the margin is viable; however, the margin is extensively involved by lymphoma, with patchy soft tissue necrosis.

Immunophenotype

Positive Markers: CD10, CD20, Bcl-6, c-Myc, PAX5, EBER ISH

Negative Markers: CD3, CD5, CD30, CD34, ALK, Bcl-2, Cyclin D1, MUM1, TdT

Ki67 highlights a proliferative index of >95%.

Cytogenetics

Not Performed

Molecular Studies

FISH testing, performed and interpreted confirms the presence of t(8;14) MYC::IgH fusion. Additionally, copy number loss of the BCL2 and BCL6 loci is noted, without evidence of rearrangement.

Proposed Diagnosis

EBV-positive aggressive B-cell lymphoma

Interesting Feature(s)

- The patient was admitted with an upper extremity injury and developed features concerning for compartment syndrome. Despite multiple serial fasciotomies with initial unknown cause, his clinical condition continued to deteriorate, necessitating emergent upper extremity amputation as a life-saving measure.
- Further investigation incidentally revealed an underlying aggressive B-cell lymphoma cells infiltrating dermis, subcutaneous adipose tissue, skeletal muscle and focally large blood vessels.
- A key and unusual aspect of this case is that the lymphoma initially presented as thoracic outlet syndrome and was misinterpreted as a hematoma on the initial CT imaging, resulting in delayed diagnosis and management.
- Ultimately, the EBV-positive aggressive B-cell lymphoma was identified incidentally in the amputated specimen

Panel Diagnosis: EBV+ Burkitt lymphoma

EA4HP26-LYWS-379

Unusual Late Relapse with T-cell/Histiocyte-rich Large B-cell lymphoma (THRLBL)-like Transformation Thirty years after treated Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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Case Description

63-year-old woman with a remote history of nodular lymphocyte-predominant Hodgkin lymphoma (details unknown) involving axillary lymph nodes at age of 33, status post radiation in remission thereafter.

She was noted to have a large left adnexal mass (~ 7.8 x 7.5 cm, SUV 14.5) with FDG avid retroperitoneal lymphadenopathy, multifocal hepatic lesions and osseous lesions on recent imaging studies, concerning for metastatic malignancy. A needle core biopsy was sampled from left common iliac lymph node for pathologic evaluation.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Histological sections show core fragments of a malignant neoplasm in a diffuse pattern. The neoplasm is composed of a few scattered large, atypical cells with irregular nuclear contours, vesicular or mummified chromatin, prominent nucleoli and variable amounts of pale eosinophilic or retracted clear cytoplasm. A subset of the neoplastic cells shows multi-lobulated popcorn cell morphology, consistent with lymphocyte-predominant (LP) cells. The inflammatory background is rich in small lymphocytes and histiocytes. Eosinophils are rare. Foci of tissue necrosis are appreciated focally.

ImmunophenotypeBy immunohistochemistry, the large neoplastic cells are positive for CD20, CD30 (weak), PAX5, OCT2, MEF2B, MUM1, and Ki-67, while negative for CD3, CD4, CD8, CD15, PD-1, ICOS and EBER (in situ hybridization). Small B cells in the background are rare, highlighted by CD20, PAX5, OCT2 stains.

The inflammatory background is T-cell rich, positive for CD3, and histiocyte-rich, positive for CD4 (weak). T cells are predominantly CD4+ T cells, with a subset expressing PD1 (small subset) and ICOS. CD8+ T cells are scattered and scant. T cells are polytypic by TRBC1 assessment.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

Lymph node, left common iliac, needle core biopsy:

Large B-cell lymphoma in a T-cell/histiocyte-rich background (THRLBCL), compatible with THRLBCL-LIKE TRANSFORMATION OF NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

Interesting Feature(s)

- The case illustrates an unusual case scenario in a woman with a remote history of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL, details unknown) diagnosed at age 33, who had been in remission after localized radiation, but experienced a relapse 30 years later.
- The presented lymphoma is an aggressive B-cell lymphoma, composed of only a few scattered large neoplastic cells (< 5%) in a T-cell and histiocyte-rich inflammatory background, resembling T-cell/Histiocyte-rich large B-cell lymphoma (THRLBL).
- Diagnostic consideration includes NLPHL, variant pattern E, and *de novo* THRLBL. In view of patient's remote history of NLPHL, the neoplasm was favored to represent a late relapse of patient's previously diagnosed NLPHL, and thus the ICC's recommendation for THRLBL-like transformation of NLPHL was adopted.
- Relapse of NLPHL after 30 years with transformation to aggressive lymphoma is highly unusual, suggesting the biological complexity of NLPHL with a broader spectrum of clinical behaviors than initially thought.

Panel Diagnosis: THRLBCL, possible late relapse of NLPB/HL

EA4HP26-LYWS-381

A challenging diagnosis between a nodular lymphocyte predominant Hodgkin lymphoma (OMS 2022) / nodular lymphocyte predominant B-cell lymphoma (ICC 2022) with CD30 heterogenous expression and altered B-cell program, and a classic Hodgkin lymphoma lymphocyte-rich subtype

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Case Description

A 51-year-old man with morbid obesity and symptomatic cholelithiasis was admitted for acute cholangitis. ERCP revealed obstructive lithiasis. A per-procedural biopsy of a hepatic pedicle lymph node was performed. Initial histology showed scant samples with rare atypical large cells (PAX5+, heterogenous positivity for CD20 and CD30, CD5-, EBV-) within a background of small lymphocytes. More representative sampling was recommended to better characterize this suspicious population. PET-CT demonstrated a disseminated hypermetabolic lymphadenopathy and a heterogeneous splenomegaly (SUVmax 16.3). A needle core biopsy was performed on a subclavicular adenopathy.

Biopsy Fixation Details

Buffered formalin

Frozen Tissue Available

Available

Details of Microscopic Findings

Histologic analysis revealed altered nodal architecture without secondary follicles. Rare large cells were scattered within a background rich in small lymphocytes with few histiocytes and no eosinophils, scleronodular fibrosis or necrosis. Large cells had a moderately abundant cytoplasm, ovoid nuclei with irregular or polylobated contours, and one or more prominent eosinophilic nucleoli.

Immunophenotype

Large cells exhibited a partial B-cell program (PAX5+ strong, CD79a+, OCT2+ faint, heterogeneous positivity for CD20, BOB1 and PU.1, CD19–, CD22–) and were CD30+ heterogeneous, CD15–, MUM1+, BCL6+, rarely EMA+ weak, IgD–, STAT6– and EBV–. These atypical B-cells were sometimes surrounded by small CD4+, CD57+, PD1+ T-cells forming rosettes mainly in residual B-cell nodular areas.

Cytogenetics

Interphase FISH using a *BCL6* break-apart probe demonstrated a gene rearrangement in large cells.

Molecular Studies

Targeted-NGS performed on the tissue sample using B-cell (36 genes) / T-cell (15 genes) lymphomas panels revealed no mutation. Cell-free analysis (cfNGS) of ctDNA (circulating tumor DNA) in peripheral blood identified low VAF variants in *DUSP2* p.G61V (3.5%), *TMSB4X* p.A8V (2.4%), and *TNFRSF14* p.C99S (3.1%).

Proposed Diagnosis

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL, WHO 2022) / Nodular lymphocyte-predominant B-cell lymphoma (NLPBL, ICC 2022), with CD30 heterogeneous expression and altered B-cell program.

Interesting Feature(s)

- In this case, we think that morphologic and immunophenotypic features alone are insufficient to definitively distinguish between classic Hodgkin lymphoma (cHL) lymphocyte-rich subtype and NLPHL/NLPBL. CD30 is usually negative in lymphocyte predominant (LP) cells, but faint to occasionally strong expression have been reported. LP cells generally preserve the B-cell program, though CD20, BOB1, OCT2 may be variably lost, and CD19 is frequently negative. PU.1 is typically positive (weak to strong) in NLPHL/NLPBL and negative in most cHL. Nuclear STAT6 expression is common in cHL but not seen in LP cells.
- However, the detection of a *BCL6* rearrangement in large cells, and a mutational profile consistent with a mature B-cell neoplasm, may favor NLPHL/NLPBL. *BCL6* gene rearrangements (translocation ~47%, amplification ~27%) may be seen in LP cells and not reported in *de novo* cHL. Cell-free ctDNA analysis may outperform tissue-based NGS in cases with scant lymphomatous cells. Recurrent variants in *DUSP2*, *JUNB*, and *SGK1* (each mutated in ~50%) may be key players in NLPHL/NLPBL pathogenesis.
- Representative tissue sampling is critical, as small biopsies may be misleading and insufficient for accurate classification.

Panel Diagnosis: NLPB/HL vs cHL

EA4HP26-LYWS-396

Marginal zone lymphoma relapse obscured by a histiocytic reactive proliferation

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Case Description

Male patient, 84 years old, with a history of nodal marginal zone lymphoma diagnosed in 2014 that presents a right axillary lymphadenopathic mass (8.5 x 6.5 cm) without other symptomatology. An excisional biopsy of the mass is performed.

Biopsy Fixation Details

Fixation with formalin 10%.

Frozen Tissue Available

Yes, OCT.

Details of Microscopic Findings

Lymph node with architecture largely replaced by a massive proliferation of histiocytes with eosinophilic, granular-appearing cytoplasm and small nuclei. No crystalloid structures are identified within the histiocytes, which are PAS-D negative. Occasional plasma cells are also identified intermingled with the histiocytes. Among the histiocytes, scattered aggregates of monotonous small lymphoid cells with scant cytoplasm are observed, accompanied by plasma cells.

Immunophenotype

The histiocytes are positive for CD68 and CD163. CD20 is positive in the cells of the lymphoplasmacytic aggregates, and CD3 highlights the accompanying T lymphocytes, which are located singly within the lymphoplasmacytic aggregates and intermingled with the histiocytes. Within the nodules, disorganized meshworks of follicular dendritic cells are identified with CD21. CD138 highlights mature plasma cells. Kappa and lambda light chains immunostains show kappa light chain restriction in the plasma cells. Intense granular kappa staining is also observed at the periphery of the histiocyte cytoplasm, whereas the lambda immunostain is negative. Immunostains for immunoglobulin heavy chains show monotypic IgM expression, with a pattern similar to that of the light chains, with granular IgM positivity at the periphery of the histiocytes, and homogeneous cytoplasmic IgG positivity in these cells, consistent with a passive, artifactual diffusion process. IgD is negative.

Cytogenetics

None.

Molecular Studies

The presence of the *MYD88* p.L265P mutation was studied by AS-PCR and was not detected.

Clonality studies were performed: an identical monoclonal *IGH* rearrangement to the observed in the NMZL diagnosed in 2014 was observed.

Proposed Diagnosis

Relapse of nodal marginal zone lymphoma with plasma cell differentiation associated with reactive histiocytosis

Interesting Feature(s)

Reactive histiocytoses associated with massive immunoglobulin production in the setting of low-grade lymphomas have been previously reported in the series by Jones D et al. and Kanagal-Shamanna R et al. (see references), among others. However, in the cases described in both series and others, the immunoglobulins were stored within the histiocytes in the form of crystalloids.

The plasmacytic differentiation is consistent with the apparent hypersecretion of IgM kappa immunoglobulins by the neoplastic cells. However, not all lymphomas with plasmacytic differentiation nor all plasma cell neoplasms exhibit this phenomenon. When it does occur, the reason why in some cases the immunoglobulins accumulate within histiocytes in the form of crystals, whereas in other cases they are observed as granules, remains a mystery.

Histiocytic proliferations can be complex to interpret even from a morphological standpoint. The presence of a small, eccentrically located nucleus in many of the histiocytes in this case, together with abundant, markedly eosinophilic cytoplasm, raised the possibility that these were rhabdoid cells or cells of that lineage.

- Jones D et al. Human Pathology. 1999;30(12):1441-8.- Kanagal-Shamanna R et al. 2016;68(4):482-91.

Panel Diagnosis: NMZL with reactive histiocytosis

CD30-positive NLPHL, patern D-E with a strong suspicion of transformation to DLBCL.

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Case Description

A 48-year-old female patient presented with a three-week history of abdominal pain. Physical examination and laboratory and radiologic evaluations revealed gallstones

Abdominal MRI demonstrated multiple calculi completely filling the gallbladder lumen

Additionally, contrast-enhancing lesions with diffusion restriction were identified in the left inguinal region measuring 6×4×7 cm; an adjacent lesion measuring 16×10 mm, and a lesion along the left external iliac tract measuring 6×3 cm. The spleen was normal

WBC 11,080/mm³, Hb 10.9 g/dL, MCV 87 fL, PLT 298,000/mm³, neu74%, lympho16.9%, and mono0.93%

Cholesistectomy was performed

Excisional biopsy of a left inguinal lymph node was obtained

Biopsy Fixation Details

The lymph node (6.5×5×2.5 cm) was sampled, fixed in formalin, and embedded in paraffin blocks.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Lymph node sections demonstrated a nodular growth pattern, with giant nodules sharply demarcated from the surrounding tissue by a fibrotic capsule

In the small nodular areas, the nodules were composed predominantly of mature lymphocytes and numerous histiocytes

In contrast, the diffuse areas contained large cells with eosinophilic cytoplasm, indistinct nucleoli, and fine vesicular chromatin

Immunophenotype

CD21/CD23 highlights a prominent follicular dendritic cell meshwork within the nodules, showing partial disruption.

CD21-positive FDC network was completely lost in the diffuse areas

The cells forming the nodules were positive for CD30, CD20, CD79a, and BOB-1, showed weak positivity for BCL-6, and were negative for PAX-5, CD10, and BCL-2

The cells in the diffuse areas were positive for CD30, CD79a, PAX-5, and BOB-1, showed weak positivity for BCL-6, were negative for CD10, and demonstrated weak BCL-2 expression in a subset of cells

The Ki-67 proliferation index was high in the residual germinal centers and ranged from 30% and 40% in both nodular and diffuse components

Cytogenetics

Not done

Molecular Studies

•FISH and NGS is pending

Proposed Diagnosis

CD30-positive NLPHL, patern D-E with a strong suspicion of transformation to DLBCL

Interesting Feature(s)

Transformation of nodular lymphocyte-predominant Hodgkin lymphoma most commonly occurs to T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), and may show partial morphological overlap. This process is typically characterized by scattered large cells within an NLPHL background and clinical disease progression. However, the presence of diffuse growth areas favors a diagnosis of diffuse large B-cell lymphoma (DLBCL) rather than THRLBCL,

particularly as diffuse lymphomas usually demonstrate a markedly higher Ki-67 proliferative index than observed in the present case. In addition, CD30 expression in NLPHL is exceedingly rare

In this case, diagnostic interpretation was challenging due to diffuse and strong CD30 expression in the B-cell population. Although CD30 positivity in NLPHL, when present, is usually confined to lymphocyte-predominant cells, the CD30-positive cells in this case co-expressed CD20, CD79a, BCL6, and BOB1, confirming B-cell lineage and excluding nonspecific staining of background histiocytes

Conversely, several histoarchitectural and immunophenotypic features supported a diagnosis of NLPHL, including a preserved CD21-positive FDC meshwork, B-cell-rich nodules, and increased CD4-positive follicular helper T-cells within the nodules. Given the increase in CD4-positive T cells, nodal T follicular helper (TFH) cell lymphoma was considered in the differential diagnosis; however, immunohistochemical staining for CD10, PD-1, CXCL13, and ICOS did not yield supportive findings

Panel Diagnosis: NLPB/HL patterns D&E, transformation to DLBCL (CD30+)

EA4HP26-LYWS-404

A Case of an EBV Positive Mucocutaneous Ulcer in the Vagina

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Case Description

The patient is a 71 year old female with a history of rheumatoid arthritis, on methotrexate and renvoq who presented with vaginal bleeding. Physical examination demonstrated a 0.5 - 1 cm vaginal lesion. A biopsy was performed.

Biopsy Fixation Details

Formalin Fixed Paraffin embeded tissue

Frozen Tissue Available

N/A

Details of Microscopic Findings

Histologic sections demonstrate fragments of tissue with overlying squamous epithelium with ulceration. The underlying dermis is completely involved by a dense atypical infiltrate. There are large cells in diffuse sheets and admixed with background inflammatory infiltrate, characterized by sheets large size with irregular nuclear contours, vesicular chromatin, single to multiple nucleoli, vacuoles and abundant pink to vacuolated cytoplasm. Focal areas with angiocentricity are noted. The background demonstrates a mixed infiltrate of small lymphocytes, plasma cells, eosinophils and neutrophils. Numerous apoptotic bodies are identified.

Immunophenotype

The lesional cells of interest stain positive with CD3 (rare cells) CD20 (rare, scattered), CD30 (most cells), MUM-1, PAX-5, CD45 RB, EBV LMP1 (rare cells) and EBV-ISH. The large abnormal cells are negative for CD4, CD5, CD7, CD8, CD10, CD15, CD68, CD163, AE1/AE3, ALK, BCL2, BCL6, CAM5.2, Cyclin D1, GMS, S100 and TdT. SMA demonstrates concentric arrangement of SMA fibers, consistent with angiocentricity. Ki-67 proliferation index is ~90%.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

EBV POSITIVE MUCOCUTANEOUS ULCER

Interesting Feature(s)

EBV-positive mucocutaneous ulcer (EBV-MCU) is a B-cell lymphoproliferative disorder that can range from a self-limiting condition to an aggressive lymphoma. First described in 2010, EBV-MCU is strongly linked to immunosuppression, particularly with the use of immunosuppressive drugs such as methotrexate.

The condition typically presents with painless or mildly painful ulcerations of the oropharyngeal mucosa, skin, or gastrointestinal tract. Histologically, the ulcers are characterized by large atypical EBV-positive, CD30-positive cells in a background of a mixed inflammatory infiltrate. The atypical cells demonstrate angiocentricity. Notably, EBV-MCU has seldom been reported in the genital region, making this a rare and unusual presentation.

Diagnosis of EBV-MCU can be challenging due to its resemblance to other lymphoproliferative disorders, particularly classic Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL).

In our case, we observe a patient on immunosuppression (methotrexate) showing large, atypical Reed-Sternberg-like cells that stain positive for CD30, PAX-5, and EBV by in situ hybridization (ISH) and EBV latent membrane protein (LMP). The cells demonstrate angiocentricity and have a background of a mixed inflammatory infiltrate. These findings are consistent with EBV-positive mucocutaneous ulcer. This is a unique case as the vaginal mucosa is a rare site for an EBV positive mucocutaneous ulcer.

Panel Diagnosis: EBV POSITIVE MUCOCUTANEOUS ULCER

EA4HP26-LYWS-409

Where Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) meets Classic Hodgkin lymphoma, lymphocyte-rich (CHL-LR) subtype: A Diagnostic Gray-Zone Case

Dr. Thi Le Na Pham, Dr. Jeffrey Schowinsky, [Dr. Jingjing Zhang](#)

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Case Description

A 42-year-old man with no significant past medical history presented with a painless, slowly enlarging subcutaneous mass of the left upper arm. Ultrasound demonstrated a hypoechoic lesion with internal vascularity measuring 1.5 × 0.9 × 1.3 cm. MRI revealed a 1.8-cm enhancing nodule in the medial subcutaneous fat approximately 13 cm proximal to the elbow. Although imaging raised concern for a soft tissue neoplasm, including sarcoma, the lesion lacked aggressive features by imaging, and a benign process was considered. The patient reported intermittent nerve-type sensations without weakness, numbness, systemic symptoms, or additional masses. The lesion was excised for definitive diagnosis.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sections show replacement of the nodal architecture by vague, expansive nodules of small lymphocytes. Germinal centers are attenuated. Within the lymphoid infiltrate are sparse, large tumor cells with occasional multilobation and prominent nucleoli. Many of the large show abundant pale cytoplasm with retraction artifact, reminiscent of lacunar cells.

Immunophenotype

Large cells are positive for CD45, CD20 (variable), Pax5 (dim to strong), CD30 (variable), CD15 (subset), CD79a (dim to moderate in a subset), BOB1, MUM1, OCT2 (strong), CD19 (variable, moderate to negative), CD22 (variable,

moderate to negative), BCL6, Ki67. Large cells are predominantly negative for EMA, CD3, EBV, BCL2, IgD. Kappa/Lambda ISH are equivocal.

CD20 and IgD highlight large B cell nodules which are sometimes interconnected, within which the majority of large atypical cells are present. CD3 highlights focal ringing of large cells. CD21 highlights intact FDC meshworks.

Cytogenetics

An abnormal clone was identified in 5 of 20 cells with a near-tetraploid karyotype:

82~94,XXYY,+X,i(1)(q10),+2,-3,-4,-6,+9,+11,+12,-15,-17,+mar,inc[cp5]/46,XY[15].

Molecular Studies

DNA Next-generation sequencing identified a TP53 p.G325V mutation (VAF 42.8%, VUS) and a ZMYM3 variant (VAF 99.6%, VUS). RNA fusion analysis was negative.

Proposed Diagnosis

Lymphoma, with a differential diagnosis for classification lying between Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and Classic Hodgkin lymphoma, lymphocyte-rich (CHL-LR) subtype.

Interesting Feature(s)

This case highlights a diagnostically challenging Hodgkin lymphoma with significant morphologic and immunophenotypic overlap between NLPHL and CHL-LR.

These findings are somewhat intermediate between NLPHL and CHL and there are atypical findings for both diagnoses. Findings in favor of CHL are CD30 and CD15 coexpression, MUM1 expression, EMA negativity, and variable expression of Pax-5. Findings in favor of NLPHL are the typical morphology with presence of large B cell nodules, strong CD20/OCT2/BOB1 expression, and variable CD30 expression. The clinical presentation also appears to favor NLPHL.

Intradepartmental review yielded differing interpretations between NLPHL and CHL-LR. Extramural consultation at two other institutes ranged from “favor NLPHL” to “NLPHL.”

The patient was treated with definitive radiotherapy to the left upper arm, resulting in complete metabolic remission. The patient is now 3 years post treatment. Surveillance imaging has continued to show remission.

Panel Diagnosis: NLPB/HL vs cHL

EA4HP26-LYWS-410

T-cell/histiocyte-rich large B-cell lymphoma-like morphology on a core biopsy

Dr. Thi Le Na Pham, Dr. Melissa Delio, [Dr. Jingjing Zhang](#)

University of Colorado Anschutz Medical Campus, Department of Surgical Pathology, Aurora, Germany

Case Description

- 68 year old male with recent presentation of acute low back pain, progressively worsening
- CT chest/abdomen/pelvis showed a well-defined relatively hyperattenuating soft tissue mass in the right paravertebral region without any obvious erosions in the adjacent L3 vertebra, splenomegaly, and prominent, though not pathologically enlarged lymph nodes in the retroperitoneum and upper abdomen
- MR cervical spine showed extensive cervical lymphadenopathy on the right side including level 2A, level 2B, level 5 and supraclavicular adenopathy.
- MR thoracic spine showed multiple metastatic lesions involving the T4, T8, T12, L1 and L2 vertebra

Biopsy Fixation Details

10% Buffered Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The core biopsy shows a predominance of small lymphoid cells with no discernable architecture. There are scattered large cells with irregular nuclear contours, cytoplasmic clearing and occasionally prominent nucleoli.

Immunophenotype

Immunostains show that the large cells are positive for CD20 (bright), CD79a, Pax5, OCT2 (bright) without small B cell nodules or much of an accompanying small B cell population. The large atypical lymphocytes are additionally positive for MUM1, BCL6 and CMYC (dim subset). The large atypical lymphocytes are negative for CD3, CD10, SOX11, CyclinD1, CD30 and EBER ISH. CD3 highlights abundant small T cells in the background. CD21 is negative, showing no meshworks. A MIB1 proliferation index highlights the majority of the large lymphocytes.

Cytogenetics

FISH is negative for rearrangements in MYC, BCL2, and BCL6. Chromosome analysis was not performed.

Molecular Studies

Not performed

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma versus Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) pattern E

Interesting Feature(s)

The findings are most suspicious for a large B cell lymphoma. The growth pattern is most consistent with T-cell/histiocyte-rich large B-cell lymphoma. Due to the nature of a core biopsy, we cannot exclude that there is diffuse growth elsewhere, or that the lymphoma actually represents pattern E Nodular lymphocyte predominant Hodgkin lymphoma. However, as several cores of the lymphoma across several sites including sampling of L3 showed an identical pattern, this likely represents an aggressive process.

Panel Diagnosis: Large B cell lymphoma consistent with NLPB/HL or THRLBCL in a limited core biopsy sample

EA4HP26-LYWS-413

Nodular lymphocyte predominant Hodgkin lymphoma in an elderly gentleman

Dr. Safa Savadi, Dr. Fatima Khan, Dr. Amer Wahed, Dr. Andy Nguyen, Dr. Hanadi Al achi, Dr. Brenda Mai

University of Texas Health Science Center Houston, Department of Pathology and Laboratory Medicine, Houston, USA

Case Description

66-year-old male with a left cervical lymph node excisional biopsy.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

Not performed

Details of Microscopic Findings

Histological sections show nodular growth with predominance of small B cells, admixed T cells, and histiocytes including epithelioid histiocytes.

There are rare single scattered large B cells (LP cells) with multilobated nuclei, single prominent or multiple nucleoli, and scant pale cytoplasm.

Immunophenotype

Positive: CD20, PAX-5, OCT-2, BCL-2 , BCL-6

Negative: CD10, CD15, CD30, Cyclin-D1, EMA, EBV-ISH

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Nodular lymphocyte predominant Hodgkin lymphoma, pattern A

Interesting Feature(s)

Morphologically, Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) overlaps with T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), but has different behavior and treatment.

The epidemiological features are interesting as this entity is commonly seen in children and young adults, although it can be seen in a wide age distribution from childhood to > 80 years

For someone this age, it was expected to be a higher grade lymphoma such as a T-cell/histiocyte-rich large B-cell lymphoma, which is often difficult to distinguish between Nodular lymphocyte predominant Hodgkin lymphoma.

Panel Diagnosis: NLPB/HL

EA4HP26-LYWS-414

T-cell/Histiocytes-Rich Large B-cell Lymphoma (THRLBCL)

Dr. Pichayut Nithagon, Dr. Ling-Lin Pai, Dr. Pooja Devi, Dr. Olga Pozdnyakova

Hospital of the University of Pennsylvania, Hematopathology, Philadelphia, USA

Case Description

History:

A 79-year-old-male with a history of hypertension, asthma, prostate cancer, splenic marginal zone lymphoma (diagnosed in 2018; underwent multiple cycles of rituximab and acalabrutinib) who presented with rising LDH levels.

Imaging (CT/PET):

Hypermetabolic lymphadenopathy above and below the diaphragm with bulky mediastinal lymphadenopathy (highest SUV of 25.1) and additional FDG avid foci in the pleura, liver, spleen, and bone. There is hepatosplenomegaly

Procedure:

Mediastinal lymph node excisional biopsy

Biopsy Fixation Details

-The specimen was collected fresh and subsequently fixed in formalin fixative.

-Fresh tissue was submitted for flow cytometric analysis.

Frozen Tissue Available

N/A

Details of Microscopic Findings

H&E stained sections show lymph node profiles with effacement of the normal architecture with a polymorphous infiltrate consisting of abundant histiocytes, lymphocytes, and scattered atypical lymphoid cells. The atypical lymphoid cells are large with irregular and sometimes multilobated nuclei, vesicular chromatin, prominent nucleoli, and scant cytoplasm.

Immunophenotype

- The large atypical CD20+ PAX5+ CD79a+ OCT2+ BCL6+ CD30+ and EBER-

- The polymorphous background cells are composed of CD3+, CD5+ T-cells, which are predominantly CD4+ with fewer CD8+ T-cells

- There are abundant CD4+ histiocytes
- CD10, BCL6, PD1, and CD57 reveal rare follicular helper T-cells.
- CD10 and BCL6 do not highlight any germinal centers.
- CD21 reveals near absence of follicular dendritic cell meshwork.

Cytogenetics

N/A

Molecular Studies

Immunoglobulin Heavy Chain Gene Rearrangement (PCR) - positive; 128bp peak

T-cell Receptor Gamma Gene Rearrangement (NGS) - negative

Next Generation Sequencing - No Disease-associated variants detected.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma.

Interesting Feature(s)

- The most striking feature of this case is the clonotypic evolution of a splenic marginal zone lymphoma into a THRLBCL. While High-grade transformation of SMZL to DLBCL occurs in approximately 5-10% of cases, transformation specifically into the THRLBCL morphologic pattern is exceedingly rare.
- Furthermore, the microenvironment in this case is atypical. Classically, THRLBCL shows a background of non-activated CD8+ cytotoxic T-cells. In our patient, the background is dominated by CD4+ T-cells. This inversion of the expected CD4:CD8 ratio likely reflects a complex interplay between clonal evolution and the iatrogenic effect of prior therapy.
- Due to the paucicellular nature of both SMZL (when diagnosed in a bone marrow sample) and THRLBCL, genetic studies for clonal relationships are exceedingly difficult and, like our case, often yield non-definitive results.
- Morphologic Mimicry: The paucity of neoplastic B cells (<10%) in THRLBCL, combined with a CD4+ background, creates a high risk for misdiagnosis as other T-cell rich lymphomas or B-cell lymphomas with rare neoplastic cells such as Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL).

Panel Diagnosis: THRLBCL

EA4HP26-LYWS-426

Crystal Storing Histocytosis Involving Bone Marrow and Leptomeninges Associated with Lymphoplasmacytic Lymphoma/Waldenstrom's macroglobulinemia

Dr. Pei Lin, Dr. Mahreen F. Hussain

UT MD Anderson Cancer Center, Hematopathology, Houston, USA

Case Description

A 72-year old woman was diagnosed with lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia in July 2022 based on a bone marrow biopsy with *MYD88*^{L265P} mutation and IgM monoclonal gammopathy (M spike: 1.4 g/dL). She was treated with Bendamustine and rituximab. In August 2023, biopsy of a paraspinal mass showed kappa restricted plasma cells without monoclonal B cells. She received radiation to the skullbase in November 2023 due to signal abnormality at the clivus concerning for lymphoma with associated double vision and headache. She started to have seizures in January 2024. Imaging studies revealed dural thickening and subdural hematoma. She continued to exhibit mental status changes with hallucinations and amnesia for a period of approximately 2 months. Furthermore, she continued to have seizures despite being maintained on lacosamide. She also developed

dizziness, gait instability, cognitive slowing, and double vision. A biopsy of left frontal dura was performed in March 2025.

Biopsy Fixation Details

Formalin fixed

Frozen Tissue Available

Not available

Details of Microscopic Findings

The biopsy of left humerus shows the marrow space is extensively replaced by numerous histiocytes with abundant cytoplasm filled with eosinophilic materials and focal extensive necrosis. There is lymphoplasmacytic infiltrate composed of small lymphoid cells and mature appearing plasma cells.

The biopsy of the right frontal dura (leptomeninges) shows extensive infiltrate of crystal storing histiocytes with rare lymphoid cells and plasma cells

Immunophenotype

Left humerus: CD163 highlights numerous histiocytes. The atypical lymphoid cells are positive for CD20 and PAX5 and negative for CD5. CD138 highlights increased plasma cells, kappa light chain restricted by kappa and lambda immunostains and express IgM. These plasma cells are negative for IgG, CD56 and cyclin D1. CD5 highlights background T cells. In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) is negative.

Leptomeninges: rare CD20+ B cells and rare CD138+ plasma cells. Numerous CD68 positive histiocytes

Cytogenetics

NA

Molecular Studies

MYD88^{L265P}

Proposed Diagnosis

Lymphoplasmacytic lymphoma/Waldenstrom Macroglobulinemia associated with crystal storing histiocytosis involving bone marrow and leptomeninges .

Interesting Feature(s)

1. Lymphoplasmacytic lymphoma/Waldenstrom Macroglobulinemia (WM) associated with crystal storing histiocytosis involving bone marrow, soft tissue and dura (CNS)
2. In contrast to the BM involvement, the CNS involvement is accompanied by few B and plasma cells, posing challenge to histological diagnosis.
3. Clinically and radiographically indistinguishable from Bing-Neal Syndrome
4. The optimal management of systemic involvement by crystal storing histiocytosis is current unknown due to its rarity.

Panel Diagnosis: LPL with crystal-storing histiocytosis

EA4HP26-LYWS-438

A 16-Year-Old Male with Mediastinal Mass and Right Axillary/Chest Swelling

Shunyou Gong

Northwestern University, Pathology, Chicago, USA

Case Description

A 16-year-old male with insulin dependent type 2 diabetes mellitus, uncontrolled glucose, presented with mediastinal mass and right axillary/chest swelling. Core biopsy of the mediastinal mass showed residual follicles and rare large

EBV-positive B cells. No treatment was given. His lymphadenopathy progressed and right axillary lymph node excisional biopsy was performed 3 months later.

Biopsy Fixation Details

Biopsy was fixed in formalin.

Frozen Tissue Available

N.A.

Details of Microscopic Findings

Mediastinal Biopsy: Histologic sections revealed residual follicles, large progressive transformation of germinal center (PTGC)-like nodules and occasional large pleomorphic cells. Some of the large pleomorphic cells had pale cytoplasm, polylobated nuclei, and prominent nucleoli, resembling "popcorn" cells, sitting within a background of numerous small lymphocytes and rare histiocytes.

Axillary LN: Histologic sections revealed diffuse infiltrate containing many large pleomorphic cells with pale cytoplasm, irregular nuclei, and prominent nucleoli, within a background of abundant histiocytes and rare small lymphocytes. A few cells had polylobated nuclei and large nucleoli, resembling "popcorn" cells. Scattered "mummified" cells are also seen.

Immunophenotype

Mediastinal Biopsy: Tumor cells were positive for CD20, PAX5, CD30, OCT2, and EBER; Tumor cells were negative for CD15.

Axillary LN: Tumor cells were positive for: CD20, PAX5, CD30, OCT2, BOB1, CD79a, CD45, and EBER; Tumor cells were negative for CD15.

Cytogenetics

N.A.

Molecular Studies

N.A.

Proposed Diagnosis

Mediastinal Mass:

- Nodular Lymphocyte-Predominant Hodgkin Lymphoma, EBV-Positive (Histologic pattern C).

Axillary lymph node:

- EBV-positive diffuse large B cell lymphoma, transformed from nodular lymphocyte-predominant Hodgkin lymphoma.

Interesting Feature(s)

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is generally EBV-negative. However, 3-5% of the NLPHL cases may contain EBV+ lymphocyte-predominant (LP) cells, and these cases often have other challenging features, difficult for diagnosis.

Six histologic patterns of NLPHL are well recognized. Histology pattern C (prominent extrafollicular L&H cells) is associated with higher clinical stages and more adverse prognosis, including transformation to more aggressive lymphoma types.

This case illustrated the evolution of a rare EBV+ NLPHL to EBV+ DLBCL.

Panel Diagnosis: NLPB/HL, EBV+?

T-cell/Histiocyte-Rich Large B-cell Lymphoma in Pediatric Patients

Dr. Gabriela Gheorghe¹, Dr. Razvan Lapadat², Dr. Maria Hintzke³

¹ Saint Jude Children's Research Hospital, Pathology, Memphis, USA; ² Pathology Specialists of Memphis, Pathology, Memphis, USA; ³ Medical College of Wisconsin, Pathology, Milwaukee, USA

Case Description

A 15-year-old, previously healthy male presented with one month of progressive back pain and weakness in the lower extremities. He denied fever, weight loss, and night sweats. CBC was unremarkable, and LDH was high at 1140IU/l (normal values: 297–537IU/l). Clinical examination revealed signs of spinal cord compression. Magnetic resonance imaging (MRI) showed an extradural mass at T5-T6.

X-ray computed tomography (CT) of the chest, abdomen, and pelvis revealed axillary and retroperitoneal adenopathy, multiple liver lesions, and splenomegaly. All lesions had positive uptake by positron emission tomography (PET). Dexamethasone was begun and the patient underwent emergent laminectomy with excision of the extradural mass. The patient was diagnosed with stage IV-A THRLBCL and was treated, as per Children's Oncology Group (COG) Protocol ANH01P1, with rituximab, prednisone, cyclophosphamide, cytosine arabinoside, doxorubicin, etoposide, and high-dose methotrexate. He was in remission 3 years after completion of therapy.

Biopsy Fixation Details

Material submitted for pathological examination including hematoxylin- and eosin-stained sections, and immunohistochemical stains.

Frozen Tissue Available

Diagnosed as Hodgkin Lymphoma

Details of Microscopic Findings

The extradural mass showed scattered large atypical cells in a background of small lymphocytes and few histiocytes. The atypical cells displayed large, lobulated nuclei with dispersed chromatin that were CD45+, CD20+, epithelial membrane antigen (EMA)+, CD3-, CD30-, and CD15-. The background cellular infiltrate showed numerous benign CD3+ T lymphocytes intermixed with few histiocytes. Large collections of histiocytes were not seen.

CD21 showed absence of a dendritic cell meshwork, confirming the diffuse nature of the process. Only rare cells were CD57+.

Bone marrow examination showed extensive involvement by a malignant process composed of similar large atypical cells in a background of benign T lymphocytes and few histiocytes.

CSF was unremarkable.

Immunophenotype

Paraspinal mass:

Atypical cells are CD45+, CD20+, epithelial membrane antigen (EMA)+, CD3-, CD30-, and CD15-.

The background cellular infiltrate showed numerous benign CD3+ T lymphocytes.

CD21 showed absence of a dendritic cell meshwork, confirming the diffuse nature of the process. Only rare cells were CD57+.

The bone marrow immunophenotype mirrors the one seen in the paraspinal mass.

Cytogenetics

Standard cytogenetics performed on the epidural mass and showed a normal male karyotype.

Molecular Studies

Molecular studies (IgH, TCR gene rearrangements) were not performed.

Proposed Diagnosis

T-cell/histiocyte-rich large B-cell lymphoma (TCHRLBCL)

Interesting Feature(s)

Presentation of TCHRLBCL as a paraspinal mass is highly unusual in the pediatric population.

Clinically neoplastic tumor, favor nonhematopoietic (Ewing's sarcoma?)

Frozen section diagnosis: Hodgkin's lymphoma

Diagnosis of TCHRLBCL was suspected in the bone marrow

Initial preliminary diagnosis of the paraspinal mass: Hodgkin's lymphoma (THRLBCL is currently under-recognized in the pediatric population; awareness of the entity and a strong degree of suspicion is required to reach the diagnosis).

Excellent prognosis even though stage 4 (as compared to adults, children respond better to therapy).

To the panel:

At the time of the submission the case was not available to take additional pictures. Case requested from the outside institution and additional pictures will be available at the time of the workshop. Furthermore, molecular studies will be performed at St Jude Children's Research Hospital to further characterise this entity.

Panel Diagnosis: THRLBCL in pediatric patient

EA4HP26-LYWS-442

EBV+ Large B-cell Lymphoma, Post-Transplant for Subcutaneous Panniculitis-Like T-cell Lymphoma

Dr. Hannah Cutshall, Dr. Rodolfo Henrich Lobo, Dr. Vijay Patel

University of Arkansas for Medical Sciences, Pathology, Little Rock, USA

Case Description

The patient is a 20-year-old female with a history of subcutaneous panniculitis-like T-cell lymphoma (SPTCL), originally diagnosed in October 2014 when she was nine years old. She completed chemotherapy in December 2017 and was in remission until August 2024, at which point she presented with a left thigh lesion. PET scan imaging at that time showed innumerable, diffusely FDG-avid cutaneous lesions. She tested positive for an *HAVCR2* mutation, for which her sister was also positive (suggesting a germline mutation). She was initially treated with romidepsin, but was refractory to treatment and therefore switched to pralatrexate. She underwent an allogeneic stem cell transplant on 7/1/2025. A PET scan performed on 9/29/2025 showed a FDG-avid, mass-like soft tissue thickening in the right posterior nasopharynx, which measured 2.3 cm and was subsequently biopsied.

Biopsy Fixation Details

Tissue was fixed in 10% formalin.

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections of the thigh lesion showed a punch biopsy with unremarkable epidermis and superficial dermis. The subcutaneous tissue showed foci of adipose tissue with fat necrosis and a mixed inflammatory infiltrate of small to medium sized lymphocytes with a subset rimming the adipocytes.

Histologic sections of the nasopharynx lesion show a mixed, predominantly mononuclear infiltrate and extensive necrosis. There are focal aggregates of medium-to-large B-cells, with at least one area of sheet-like proliferation as well as areas of markedly increased/loosely aggregated plasma cells, which appear kappa-predominant/restricted by kappa/lambda ISH.

Hemophagocytic histiocytes were identified on the bone marrow biopsies performed both at the time of diagnosis and at the time of Large B-cell lymphoma presentation.

Immunophenotype

The atypical lymphocytes in the thigh lesion were positive for CD2, CD3, CD5, CD8, TIA and Granzyme B, while negative for CD4, CD25, CD56, CD30 and EBER.

The atypical lymphocytes in the nasopharynx lesion were positive for CD20, EBER, a subset CD138 and showed kappa restriction.

Cytogenetics

Cytogenetics performed on the bone marrow biopsy showed a normal female karyotype. Cytogenetic studies performed on the nasopharyngeal tissue showed no growth.

Molecular Studies

NGS showed a homozygous mutation in HAVCR2.

Proposed Diagnosis

Large B-cell lymphoma, EBV+, compatible with post-transplant lymphoproliferative disorder (s/p allogeneic stem cell transplant for subcutaneous panniculitis-like T-cell lymphoma).

Interesting Feature(s)

This is an unusual case of an EBV+ large B-cell lymphoma that presented as a nasopharynx lesion, following an allogeneic stem cell transplant for subcutaneous panniculitis-like T-cell lymphoma.

The original diagnosis of subcutaneous panniculitis-like T-cell lymphoma represents a rare, more aggressive form of the disease with a germline mutation in *HAVCR2* (which is often associated with hemophagocytic lymphohistiocytosis).

Panel Diagnosis: PTLD, EBV+ DLBCL

EA4HP26-LYWS-449

TCHRLBCL Inguinal Lymph Node

Dr. Matan D. Kadosh, Dr. Vrinda Shenoy, Dr. Wen Fan

Mount Sinai Morningside/West, Pathology, New York, USA

Case Description

•37-year-old male with past medical history of pancytopenia 5 months before and now presented with fever and drenching night sweats for two weeks. Recent bone marrow as diagnosed as Nodular Lymphocyte Predominant Hodgkin's Lymphoma.

•CT chest abdomen pelvis with contrast on admission:

•Hepatosplenomegaly (up to 22 cm)with diffuse innumerable hepatic and splenic hypodensities (splenomegaly up to 24 cm) and diffuse lymphadenopathy highly concerning for hematologic malignancy including lymphoma.

•Otherwise, diffuse lymphadenopathy.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

There is diffuse vaguely nodular effacement of the tissue architecture. At low magnification, the involved tissue has a characteristic pale eosinophilic appearance attributable to the background histiocytic population that is also mixed with increased small lymphocytes. The neoplastic large cells are scattered without formation of tight aggregates or confluent sheets.

Immunophenotype

The neoplastic cells express pan-B-cell markers CD20, PAX5, OCT-2, BOB-1, IMP-3 and BCL6, and variably express MUM1 and CD30(faint focally) and negative for CD10 and bcl-1. IHC for EBER is negative. The background contains high numbers of CD68+. CD163+ as well as CD3+, CD5+ T cells. Characteristically, there is a scanty small

B cells in the background. Follicular dendritic cell meshwork (CD21+ or CD23+) are absent. The case was the subject for intradepartmental consultation with consensus.

Cytogenetics

Normal Male Karyotype, XY.

Molecular Studies

N/A

Proposed Diagnosis

High grade B-cell lymphoma consistent with T-cell/histiocyte-rich large B-cell lymphoma.

Interesting Feature(s)

- The patient had a history of Nodular lymphocyte predominant Hodgkin's lymphoma in the bone marrow that progressed over 5 months to present as T-cell/histiocyte-rich large B-cell lymphoma, PMID: 31287335.
- The patient was treated at first with RCHOP with no improvement.
- This case shows that close follow up and extensive diagnostic multi-disciplinary approach is needed for successful outcomes.

Panel Diagnosis: NLPB/HL, pattern E

LYMPHOMA SESSION III | Immune privileged site lymphomas excluding primary diffuse large B-cell lymphoma (DLBCL) of the brain parenchyma and testis (i.e. primary lymphomas of the ovary, adrenal gland, breast, meninges)

EA4HP26-LYWS-9	A challenging case of B-cell lymphoma presenting as meningioma
EA4HP26-LYWS-16	Primary T-cell lymphoma of central nervous system.
EA4HP26-LYWS-36	Primary DLBCL of the adrenal gland showing a genetic MCD profile
EA4HP26-LYWS-40	Primary breast high-grade B-cell lymphoma with blastoid morphology: HGBCL, NOS (with <i>MYC</i> and <i>BCL6</i> rearrangements)/ HGBCL with <i>MYC</i> and <i>BCL6</i> rearrangements (double-hit lymphoma) with EBV ?reactivation
EA4HP26-LYWS-76	Breast Implant–Associated Anaplastic Large Cell Lymphoma With Near-Complete Loss of T-Cell Markers and Aberrant CD79a Expression
EA4HP26-LYWS-90	Fluid-overload large B-cell lymphoma (FO-LBCL), with an MCD-like molecular profile
EA4HP26-LYWS-102	Primary cerebral low-grade B-cell lymphoma with plasmacytic differentiation, associated with AL (lambda)-type amyloid deposition
EA4HP26-LYWS-106	Extranasal Presentation of an Extranodal NK/T-cell Lymphoma
EA4HP26-LYWS-107	Bilateral Adrenal Diffuse Large B-cell Lymphoma with Multisite Endocrine Involvement
EA4HP26-LYWS-150	Primary ovarian large B-cell lymphoma of ABC and C5/MCD subtypes with systemic relapse.
EA4HP26-LYWS-157	Primary breast DLBCL initially presenting as CNS Lymphoma
EA4HP26-LYWS-188	Primary Large B-Cell Lymphoma of the Adrenal Glands (immune-privileged site) in a patient with Agent Orange Exposure
EA4HP26-LYWS-195	A case of donor-derived primary central nervous system peripheral T-cell lymphoma, not otherwise specified
EA4HP26-LYWS-208	Case Number: LYWS-208 Primary Large B-cell Lymphoma of the Meninges (Immune-Privileged Site) Presenting as Meningioma
EA4HP26-LYWS-209	Primary testicular B-lymphoblastic lymphoma with novel <i>PAX5::BPIFB2</i> fusion
EA4HP26-LYWS-224	Bilateral primary Adrenal Diffuse large B cell lymphoma
EA4HP26-LYWS-234	EBV-positive NK/T-cell lymphoma of the testis
EA4HP26-LYWS-248	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with prominent plasma cell differentiation of the cranial dura: a case report
EA4HP26-LYWS-250	EBV-positive extranodal NK/T-cell lymphoma presenting as uveitis and bilateral adrenal masses
EA4HP26-LYWS-258	Diffuse large B-cell lymphoma of the CNS involving the nasopharynx
EA4HP26-LYWS-259	Primary Ovarian Lymphoma Mimicking Sex Cord Stromal Tumor
EA4HP26-LYWS-260	Immune privileged site lymphoma of the meninges
EA4HP26-LYWS-264	Aggressive NK cell lymphoma involving the CNS with associated hemophagocytic lymphohistiocytosis
EA4HP26-LYWS-274	High-grade B-cell lymphoma presenting as bilateral adrenal lesions in a post-solid-organ transplantation setting

EA4HP26-LYWS-292	Intrathyroidal Diffuse Large B-Cell Lymphoma, anaplastic variant.
EA4HP26-LYWS-305	Intrathyroidal Follicular Lymphoma, CD23+; BCL2-
EA4HP26-LYWS-307	Peripheral T-cell Lymphoma Arising in Testis with CNS Involvement
EA4HP26-LYWS-316	Leptomeningeal Marginal Zone Lymphoma with AL (kappa)-type Amyloidosis
EA4HP26-LYWS-346	Dural Marginal Zone Lymphoma
EA4HP26-LYWS-348	Primary ovarian diffuse large B-cell lymphoma with CDKN2A mutation
EA4HP26-LYWS-350	Testicular pleomorphic mantle cell lymphoma versus DLBCL with CCND1 rearrangement
EA4HP26-LYWS-362	EBV+ DLBCL of the Ovary
EA4HP26-LYWS-364	Intravascular Large B-cell lymphoma
EA4HP26-LYWS-369	Primary Breast Follicular Lymphoma with BCL2 Expression and Without BCL2 or BCL6 Rearrangement
EA4HP26-LYWS-371	An Atypical Uterine Lymphoproliferation in a Transsexual Patient
EA4HP26-LYWS-375	Diffuse Large B-Cell Lymphoma of the Ovary: Immune-Evasion Biology Beyond CNS and Testis
EA4HP26-LYWS-393	Primary Dural Follicular Lymphoma
EA4HP26-LYWS-397	Primary breast large B cell lymphoma with MYD88 mutation.
EA4HP26-LYWS-417	Primary Extranodal Marginal Zone B cell lymphoma of the Left Ovary with involvement of Left fallopian tube and Left Anterior Endomyometrium.
EA4HP26-LYWS-430	Primary Diffuse Large B cell Lymphoma arising as a primary ovarian neoplasm
EA4HP26-LYWS-436	Don't forget CD20 in breast implant-associated lymphoma
EA4HP26-LYWS-445	Primary Adrenal Diffuse Large B Cell Lymphoma
EA4HP26-LYWS-446	Primary Breast DLBCL with Double Expressor Phenotype in a Patient with Hepatitis C History

A challenging case of B-cell lymphoma presenting as meningioma

Dr. Zachary High^{1,2}, Dr. Nana Matsumoto^{1,2}, Dr. Scott Kulich^{1,3}, Dr. Majd Jawad^{1,2}

¹ University of Pittsburgh, School of Medicine, Pittsburgh, USA; ² University of Pittsburgh Medical Center (UPMC), Department of Pathology, Division of Hematopathology, Pittsburgh, USA; ³ University of Pittsburgh Medical Center (UPMC), Department of Pathology, Division of Neuropathology, Pittsburgh, USA

Case Description

A 56-year-old man with history of hypothyroidism and tobacco use presented with progressive right-sided vision loss over 3 months. Initially, he was found to have bilateral cataracts and underwent left eye surgery, which resulted in improved vision in that eye. A few weeks later, he underwent right eye cataract surgery but experienced persistent visual disturbances in the right eye, along with transient numbness of the right arm and leg. Skull-base MRI imaging demonstrated a 2.6 cm enhancing T2 hyperintense mass centered in the right anterior clinoid process, causing displacement of the right optic nerve and radiologically consistent with meningioma. He subsequently underwent endonasal resection of the tumor.

Biopsy Fixation Details

10% neutral phosphate-buffered formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

Submitted tissue was involved by diffuse lymphocytic infiltrate with crush artifact. Lymphocytes were composed of many small cells with dense chromatin, inconspicuous nucleoli and scant cytoplasm, admixed with occasional plasma cells and scattered, loosely aggregated intermediate to large lymphoid cells with dispersed chromatin, small nucleoli, and moderate pale cytoplasm with retraction artifact. A subsequent cerebrospinal fluid (CSF) cytologic examination similarly demonstrated a mixture of small and large lymphocytes with occasional plasma cells.

Immunophenotype

By immunohistochemistry, CD20 and PAX5 were positive in both small and large B cells. B cells outside of the germinal centers were negative for CD10, CD15, CD30, ALK1, BCL6, BRAF, or Cyclin D1. CD5 and CD43 were difficult to interpret given the background T cells; however, in B cell-rich areas, they were negative. B cells showed lambda light chain restriction by in situ hybridization (ISH), with a plasmacytic component. CD10 and BCL6 highlighted few germinal centers that were negative for BCL2. Ki-67 ranged between 40-60%. No increase in IgG4/IgG positive cells noted. EBER-ISH was negative. Flow cytometry revealed polytypic B cells without overt aberrancy and T cells were normal. Limited flow cytometric studies on the CSF similarly showed polytypic B cells and few CD19 positive plasma cells with indeterminate surface light chain expression.

Cytogenetics

Not performed.

Molecular Studies

B cell gene receptor studies by PCR were positive for clonal gene rearrangements (Peaks: IgK-VJ, 283bp, IgK-DE, 236bp and 275bp) by BIOMED2 PCR. MYD88 L265P mutational analysis by PCR was negative.

Proposed Diagnosis

B cell lymphoma, favor marginal zone lymphoma with increased large cells.

Interesting Feature(s)

We present a rare case of dural based B cell lymphoma, radiologically mimicking meningioma. Primary dural lymphomas are different biologically from other CNS lymphomas and are usually low-grade marginal zone lymphomas (MZL), unlike other primary CNS lymphomas that are commonly diffuse large or high grade B-cell lymphomas. Histologic subclassification in this case was challenging due to the increased number of large cells, in a background of small lymphocytes and plasma cells. The polytypic B cell pattern by flow cytometry was unusual and

might be attributed to a rich inflammatory background or a sampling bias. There were no diffuse or large aggregates of large cells, and therefore marginal zone lymphoma with increased large cells was favored. Studies have shown that MZL with increased large cells may carry a similar overall survival to MZL without increased large cells, however MZL with increased large cells is more likely to transform to large cell lymphoma.

Panel Diagnosis: extranodal MZL

EA4HP26-LYWS-16

Primary T-cell lymphoma of central nervous system.

Dr. Akeem Giles, Dr. Elisa Lin, Dr. Kikkeri Naresh, Dr. Jason Love, M.Sc./M.A. Xiaobing Ren, Dr. Jonathan Fromm, **Dr. Alireza Torabi**

University of Washington, Department of lab and medical pathology, seattle, USA

Case Description

45-year-old female with no significant past medical history, presented with episodic worsening memory and speech difficulty for which she underwent an MRI that revealed a heterogeneously enhancing 4 x 3 x 2.7 cm mass in the posterior temporoparietal region with profound cytotoxic edema and central necrosis. PET scan showed no evidence of extracranial disease. She underwent subtotal debulking of the tumor.

Biopsy Fixation Details

Formalin Fixed

Frozen Tissue Available

No

Details of Microscopic Findings

H&E staining demonstrates small-medium sized lymphocytic infiltrate with minimal cytoplasm, irregular contours, frequent notching, and condensed chromatin. No sheets of large cells identified. Mitotic activity is noted at up to 7 mitotic figures in 10 high-power fields. Apoptotic bodies are frequent.

Immunophenotype

Flow cytometry identified an abnormal T-cell population, representing 29% of the white cells that was positive for CD2, CD5, CD7 (subset), CD38 (dim), and CD45 without surface CD3, CD4, CD8, CD10, CD19, CD20, CD30, CD34, significant CD56, CD138, CD200, and surface or cytoplasmic immunoglobulin light chains. Additionally, immunostain showed positivity for CD3 (cytoplasmic), TIA1 and negative for TCR-beta F1 and TCD delta. Ki67 showed proliferation index of 10-20% and TdT was negative. In-situ hybridization for EBV-RNA was negative.

Cytogenetics

Not done on the brain biopsy tissue.

Bone marrow biopsy staging was negative for involvement by T-cell lymphoma by morphology, but cytogenetic showed 46,XX,del(17)(q25)[3]/46,XX[27].

Molecular Studies

Brain tissue: T-cell clonality for TCR-gamma chain showed a clonal population and lymphoid targeted gene sequencing was negative.

Proposed Diagnosis

Primary T-cell lymphoma of the central nervous system (immunoprevilaged site).

Interesting Feature(s)

Primary T-cell lymphoma in the brain is rare. This case showed no expression of TCR a/b or g/d. Based on the Codex system and expression of TBX21 and CXCR3, this is most likely TBX21 subtype.

EA4HP26-LYWS-36

Primary DLBCL of the adrenal gland showing a genetic MCD profile

Thomas Menter

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Case Description

In August 2025, the 79 years old male patient was hospitalized in a hypertensive crisis aggravated by cerebral hemorrhage. In a CT scan, a lesion of the left adrenal gland (diamater 59 mm) was diagnosed. The lesion was resected.

Past medical history:

chronic renal insufficiency KDIGO G2 A1

Vitamine B12 deficiency

Biopsy Fixation Details

The tissue was fixed in 4% buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

There is a diffuse infiltrate of blastoid cells infiltrating the adrenal gland and the surrounding adipose tissue.

Immunophenotype

The lesional cells were positive for CD20, BCL2, MUM1 and BCL 6. They were negative for CD5, CD10, c-Myc and EBER.

Cytogenetics

There was no rearrangement of the MYC locus by FISH analysis (break apart probe).

Molecular Studies

HTS using a customized panel comprising 172 lymphoma related genes was performed. The subsequent pathogenic mutations were found:

MYD88: p.L265P (21%)

CD79B: p.Y197C (48%)

BTG1: c.130_148+6del Splice Site Intron 1

PIM1: p.A10V (30%)

PIM1: p.E135K (29%)

PIM1: p.V96L (29%)

PIM1: p.G28D (16%)

BCL7A: c.92+1G>A (22%) Splice Site in Intron 1

Furthermore, 20 VUS were discovered, the case showed the genetic signature of somatic hypermutations.

Proposed Diagnosis

Primary DLBCL, NOS of the adrenal gland

COO-classification: non-GCB type (Hans algorithm)

MCD-Subtype (LymphGen-algorithm)

Interesting Feature(s)

- According to the PET scan, there is only an infiltration of the adrenal gland (Stage I E).
- This case supports the theory of a distinct group of DLBCLs with a specific genotype ("MCD") occurring in distinct localizations ("immune sanctuaries").

•Due to further genetic subtyping, the patient was put on R-CHP with the addition of Polatuzumab due to an increased risk of an aggressive course of the disease.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-40

Primary breast high-grade B-cell lymphoma with blastoid morphology: HGBCL, NOS (with *MYC* and *BCL6* rearrangements)/ HGBCL with *MYC* and *BCL6* rearrangements (double-hit lymphoma) with EBV ?reactivation

Dr. Gorana Gasljevic^{1,3}, PhD/MD student Panna Dora¹, PhD/MD Vida Stegel²

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Case Description

43-yrs-old female patient, otherwise healthy. Rapidly growing tumor in left breast measuring 6 cm, no enlarged peripheral lymph nodes. No B-symptoms. Fine needle aspiration: High-grade B cell lymphoma. Laboratory results at admission: L 5x10⁹/L, Hbg 127 g/L, Plt 240x10⁹, LDH 3.57 ukat/L (normal <4.12). HVC, HVB and HIV serology negative. Clinical stage I.E.A, according to Murphy I. PET-CT performed only after the excisional biopsy: increased activity in the area of previous surgery with SUV 3.5, no other foci of increased metabolic activity anywhere in the body. CTs of the neck, thorax, abdomen normal. Cerebrospinal fluid cytologically negative. Treated as BL with chemotherapy according to BFM protocol with intrathecal administration of methotrexate, 4 cycles until October 2023. Inter-rim PET CT: complete remission. Adjuvant radiotherapy of the left breast 30.6 Gy until November 2023. Last clinical control in the end of October 2025: no signs of relaps.

Biopsy Fixation Details

10% buffered formalin overnight

Frozen Tissue Available

Yes

Details of Microscopic Findings

Diffuse infiltration by medium sized, atypical, blastoid looking lymphatic cells with finely dispersed chromatin and small rim of cytoplasm. Numerous mitoses with many tingible body macrophages and starry sky pattern.

Immunophenotype

Positive for CD20, BCL2 (100%), BCL6 (100%), CD10, c-myc (100%). EBV-ISH rare, dispersed EBV positive cells (<5%), negative LMP1 and EBNA2. Negative CD3, CD30, TdT, CD5, cycline D1, CD34.

Cytogenetics

Translocations of *MYC* and *BCL6* (*MYC* and *BCL6* break-apart probes). *BCL2* translocation not present. *BCL6:MYC* dual fusion probe was not tested.

Molecular Studies

TruSight Oncology 500 DNA kit Illumina

XPO1 E571K (c.1711G>A, p.Glu571Lys) VAF 29% -gain of function and oncogenic according to OncoKB database
Loss of 3q13.33 (*GSK3B*), 6p22. (*HLA-A*), 9p21.3 (*CDKN2A*, *CDKN2B*), 10q21.2 (*ARID5B*)

Gain of 12p13.33-12p11.21(*KDM5A*, *FGF23*, *FGF6*, *CHD4*, *ETV6*, *KRAS*, *H3F3C*), 12q12-12q15 (*ARID2*, *KMT2D*, *ERBB3*, *NAB2*, *CDK4*, *MDM2*), 18q21.1-18q21.33 (*SMAD2*, *SMAD4*, *MALT1*, *PMAIP1*, *BCL2*)

Proposed Diagnosis

WHO5: Primary breast high-grade B-cell lymphoma, NOS (with *MYC* and *BCL6* rearrangements) and EBV ?reactivation

ICC2022: Primary breast high-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements (double-hit lymphoma HGBCL-DH-*BCL6*) and EBV ?reactivation

Interesting Feature(s)

Extranodal location, blastoid morphology, myc-rearrangement and occasional EBV-positive lymphoma cells could point the differential diagnosis toward Burkitt lymphoma (BL) (virus might be implicated through a “hit-and-run” mechanism) but strong *BCL2* expression is against this diagnosis. As well, molecular profile better fits to the diagnosis of HGBCL, NOS/DH than BL (20–40% of *MYC/BCL6* double-hit lymphomas show *CDKN2A/CDKN2B* co-deletion while it is usually not present in BL). It is questionable if EBV infection can be a secondary event. B-lymphoblastic lymphoma was excluded by negative reactions to CD34 and TdT, blastoid MCL was excluded by negative reactions to CD5 and Cyclin D1 and high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements was excluded by lack of *BCL2* translocation. Approximately 30% of HGBCL-DH-*BCL6* are so called »pseudo-double hit lymphomas« due to t(3;8)(q27;q24) with consequent *BCL6-MYC* fusion that are associated with a germinal center immunophenotype, extranodal involvement and frequent *BCL2* translocations.

Panel Diagnosis: HGBL with *MYC* and *BCL6* rearrangements

EA4HP26-LYWS-76

Breast Implant–Associated Anaplastic Large Cell Lymphoma With Near-Complete Loss of T-Cell Markers and Aberrant CD79a Expression

Dr. Xin Duan, Dr. Lisa Yuen

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Case Description

A 74-year-old woman underwent bilateral mastectomy and implant reconstruction 25 years ago for lobular carcinoma in situ. She presented with progressive right breast capsular contracture and breast enlargement for 6 months. Bilateral capsulectomies showed chronic inflammation without malignancy. Within weeks, she developed recurrent right breast swelling. PET/CT revealed a 9 cm FDG-avid mass in the right mastectomy bed with chest wall invasion and possible pleural extension. Drainage of the right breast yielded gelatinous fluid with rubbery tan-gray soft tissue fragments. After a diagnosis was established, the patient was treated with chemotherapy (CHOP) followed by immunotherapy (brentuximab-CHP).

Biopsy Fixation Details

- 1) FFPE of the right breast capsule
- 2) FFPE of the diagnostic right breast fluid/soft tissue

Frozen Tissue Available

N/A

Details of Microscopic Findings

- 1) Representative sections from the right breast capsulectomy specimen showed a dense fibrous capsule with lymphohistiocytic chronic inflammation. No large atypical cells were seen.
- 2) Sections from the right breast fluid/soft tissue specimen showed fragments of tissue involved by a diffuse infiltrate of large atypical lymphoid cells, which were highly pleomorphic with irregular nuclei, open chromatin, prominent nucleoli, and moderately abundant eosinophilic cytoplasm. Frequent hallmark cells, mitotic figures, and apoptotic bodies were seen.

Immunophenotype

- 1) The breast implant capsule showed a mixture of CD3+ T cells and CD20+ B cells.
- 2) The neoplastic cells were positive for CD30 (strong diffuse membranous and golgi staining), CD4, granzyme (subset), CD2 (weak/subset), CD79a (diffuse weak cytoplasmic staining), BCL6, BCL2 (weak/subset), MUM1, EMA, and MYC (70%), and were negative for CD20, CD5, CD7, CD8, PAX5, ALK1, CD43, CD10, CD138, and cyclin D1. CD3 was focally weakly positive. Ki67 showed a high proliferation rate of 90%.

Cytogenetics

N/A

Molecular Studies

T Cell Receptor Gamma (TCRG) T-cell clonality assay showed two clonal rearrangements. The primary rearrangement involved the TRG Vg2 and JgP2 gene segments and accounted for 55.46% of total sequencing reads, while a second rearrangement utilizing TRG Vg4 and Jg1/2 comprised 25.65% of total reads.

Proposed Diagnosis

Breast implant-associated anaplastic large cell lymphoma

Interesting Feature(s)

The patient's clinical presentation and course is characteristic of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL); however, this case demonstrates two diagnostically challenging features. First, the neoplastic cells show an almost complete loss of pan-T-cell marker expression, including absence of CD5 and CD7, and focal weak positivity for CD3 and CD2. CD79a showed diffuse non-specific staining, a known pitfall that may suggest B-cell lineage in limited specimens. TCR gene rearrangement studies were essential to establish T-cell lineage, underscoring the critical role of molecular studies in immunophenotypically ambiguous BIA-ALCL. Second, the initial capsulectomy specimen was negative for lymphoma, likely reflecting sampling limitations. BIA-ALCL usually shows focal or patchy involvement of the fibrous capsule and may be predominantly effusion-based, necessitating extensive capsule submission and thorough evaluation of seroma fluid for optimal diagnostic sensitivity. Collectively, these findings highlight the importance of comprehensive immunophenotypic, molecular, and sampling approaches to avoid underdiagnosis.

Panel Diagnosis: breast-implant associated ALCL

EA4HP26-LYWS-90

Fluid-overload large B-cell lymphoma (FO-LBCL), with an MCD-like molecular profile

Dr. Yeseul Kim¹, Dr. Taesung Jeon²

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Case Description

A 98-year-old woman with hypertension and diabetes mellitus; past history of bladder cancer treated by TURBT. She presented with dyspnea. Chest CT revealed a large pericardial effusion and a left pleural effusion. Pleural fluid was obtained via chest tube drainage. Abdomen and brain CT showed no mass lesion or lymphadenopathy.

Biopsy Fixation Details

Cytology slides were prepared using the SurePath™ liquid-based cytology (LBC) method (BD Diagnostics). The residual specimen was formalin-fixed and paraffin-embedded to generate a cell block for ancillary studies.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Cytologic preparations showed numerous large atypical lymphoid cells with plasmablastic morphology, including marked nuclear pleomorphism, vesicular chromatin, prominent nucleoli, a high nuclear-to-cytoplasmic ratio, and amphophilic cytoplasm. Karyorrhectic debris and frequent mitotic figures were present.

Immunophenotype

CD2 positive; CD3 negative; CD4 negative; CD5 positive; CD7 negative; CD8 negative; CD20 positive; CD79a positive; PAX5 positive; BOB1 positive; OCT2 positive; CD30 negative; CD10 negative; BCL6 negative; BCL2 negative; MYC negative; MUM1 positive; CD138 negative; Ki-67 ~90%; HHV8 negative; EBER in situ hybridization negative.

Cytogenetics

Not performed.

Molecular Studies

- IGH gene rearrangement: positive.
- TCR- β gene rearrangement: negative.
- TCR- γ gene rearrangement: negative.
- Targeted NGS (Lymphoma panel)
 - SNV/Indel: CD79B mutation, KMT2D truncation, PIM1 mutation, ABCG2 mutation, ATRX truncation, CDH1 mutation
 - Copy-number variation : FOXP1, PAX5 and POU2F2 copy number gain
- The overall molecular profile was interpreted as suggestive of an MCD-like subtype by LymphGen 2.0.

Proposed Diagnosis

Fluid-overload large B-cell lymphoma (FO-LBCL), with an MCD-like molecular profile

Interesting Feature(s)

This FO-LBCL shows a molecular pattern resembling the MCD subtype (notably including CD79B and PIM1 alterations). The case raises the question of whether serous cavities such as the pleural and pericardial spaces may function as an “immune-privileged–like” microenvironment, analogous to classic immune-privileged sites (e.g., CNS or testis), potentially contributing to this molecular phenotype.

Panel Diagnosis: fluid overload LBCL

EA4HP26-LYWS-102

Primary cerebral low-grade B-cell lymphoma with plasmacytic differentiation, associated with AL (lambda)-type amyloid deposition

PhD/MD Yi Zhu¹, PhD/MD Kevin B. Long², PhD/MD Derek R. Johnson³, PhD/MD M. Adelita Vizcaino¹, PhD/MD Ellen D. McPhail¹, PhD/MD Dan P. Larson¹, PhD/MD Caterina Giannini¹

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Case Description

The patient is a 39-year-old man with a history of multiple sclerosis diagnosed more than 10 years ago. He reports no significant symptoms attributable to multiple sclerosis aside from mild language difficulty. Brain Magnetic Resonance Imaging (MRI) demonstrates multiple stable periventricular white matter lesions consistent with a demyelinating process, as well as a cystic T2-hyperintense lesion in the deep left frontal lobe white matter extending to the periventricular region, with associated patchy enhancement. This lesion was first identified 5 years ago and demonstrated slow progression. After biopsy, the patient underwent Gamma Knife radiosurgery. Follow-up imaging over 3 years shows no evidence of recurrence or progression.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The biopsy demonstrates fragments of cerebral cortex and subcortical white matter with a predominantly perivascular lymphoplasmacytic infiltrate composed of small lymphocytes and mature-appearing plasma cells. Scattered within perivascular spaces and the surrounding parenchyma are several globular foci of lamellated eosinophilic material that is Congo red-positive. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) detects a peptide profile consistent with AL (lambda)-type amyloid deposition.

Immunophenotype

The lymphoid infiltrate consists predominantly of CD20-positive B cells with admixed CD138-positive plasma cells and fewer CD3-positive T cells. B cells lack expression of CD5, CD10, and Cyclin D1. In situ hybridization for kappa and lambda light chain mRNA demonstrates lambda light chain restriction within plasma cells. Epstein-Barr virus (EBV) in situ hybridization is negative.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Primary cerebral low-grade B-cell lymphoma with plasmacytic differentiation, associated with AL (lambda)-type amyloid deposition

Interesting Feature(s)

Low-grade B-cell lymphomas primarily involving brain parenchyma are extremely rare. The findings of this case favor marginal zone lymphoma (MZL), the most common subtype, which typically exhibit lambda light-chain restriction. These tumors generally have an insidious onset, often with a prolonged history of symptoms before diagnosis. AL (lambda)-type amyloid deposition may occur in the brain as a cerebral amyloidoma, which is usually a localized process associated with an underlying clonal B-cell population and a stable, indolent clinical course. A lamellated globular appearance of amyloid as seen in this case is also unusual.

Panel Diagnosis: extranodal MZL

EA4HP26-LYWS-106**Extranasal Presentation of an Extranodal NK/T-cell Lymphoma**

Dr. Ahmed Ayad, Dr. Pallavi Galera, Dr. Yanming Zhang, Dr. Ahmet Dogan, **Dr. Nicholas J. Barasch**

Memorial Sloan Kettering Cancer Center, Hematopathology, New York City, USA

Case Description

A 33-year-old female with an 8-month history of a 4.5 cm mobile breast mass and night sweats presented without weight or appetite change, fevers, chills or palpable adenopathy; however, the patient reports new onset right arm swelling without ulceration or discoloration. Following lumpectomy confirming lymphoma, a staging PET/CT scan revealed limited adenopathy in Waldeyer's ring, a left level 1B node (1.0 cm, SUV 5.1) and left thoracic lymphadenopathy (1.1 cm, SUV 8.9) as well as suspicious hypermetabolic soft tissue lesions in the right medial biceps, right antecubital subcutaneous tissue and around the right distal radius (SUV 17.8). Diffuse marrow uptake (SUV 2.6) and post-surgical uptake in the right breast (SUV 5.9) were also noted. There is no hepatosplenomegaly. Nasopharyngeal lesions were absent. Flow cytometry of peripheral blood, CSF, and bone

marrow biopsy were negative for the lymphoma. An EBV quantitative assay was 76.8 IU/mL (ref <=35.0 IU/mL); HTLV-I/-II, HBV, HCV, and HIV were negative. No autoimmune disease history. SMILE regimen was initiated resulting in PET/CT resolution after two cycles.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections show a diffuse, dense proliferation forming nodules and sheets infiltrating dense fibrous tissue with occasional residual follicles with germinal centers. Necrosis is absent. The infiltrate is composed of atypical mostly medium-sized cells with occasional larger cells admixed with small lymphocytes, plasma cells, and histiocytes. The atypical cells have irregularly folded nuclei and a variably moderate to small amount of pale to clear cytoplasm. The chromatin is granular to vesicular, and nucleoli are identified. Mitotic figures are readily seen.

Immunophenotype

Expression: CD3 (at least cytoplasmic), CD2, CD94, TIA1, EBER-ISH, BCL-2, ATM (retained but partial dim), B2M, HLA-1

Partial: LEF1 (weak), c-MYC, Ki67 (40-50%)

Equivocal: p53 (likely WT)

Negative: CD5, CD7, CD4, CD8, CD56, CD57, granzyme, TCR-alpha, TCR-beta, TCR-delta, CD68 (KP1), MUM1, CD20, CCR4, CXCL13, ICOS, BCL6, CD10, EBV-LMP, TRBC1, CD25, TCL 1A, Cyclin D1, ALK1, CD30, HHV-8, PAX-5, CD22, CD19, CD79a, TDT, CD1A, CD163, CD21, CD23, CIITA, HLA-DR, PD-L1, PD-L2, PD-1
CD21 and CD23 highlight few preserved and residual FDC meshworks in B-cell rich areas.

Cytogenetics

SNParray: Gains in 1q43-qter, 7q and 8 and loss in 7p, segment 9q13-q31.1, segment 11q22.3-q23.2 (including the *ATM* gene), 12q21.1-q23.3 and X.

Molecular Studies

9 somatic mutations identified with variant allele fractions of 15%-

25% including *CIC*, *FANCM*, *FBXO11*, *H3C8*, *ROBO1*, *RPS15* and *SRCAP* are identified. A truncating mutation in *CIITA* and splicing variant in *TNFAIP3* is identified. No gene fusions by RNA sequencing. No clonal rearrangement involving the TCR Beta, TCR Gamma or IG Heavy Chain genes.

Proposed Diagnosis

Extranodal NK/T cell lymphoma (ENKTL)

Interesting Feature(s)

This case represents an unusual site of presentation for this disease. The limited adenopathy and extranodal avidity by PET/CT scanning supports an extranodal classification despite unusual distribution. The presence of CD94 expression with a lack of molecular T-cell clonality and the absence of T-Cell receptor proteins (alpha/beta/delta) supports a more NK phenotype despite absence of CD7 and CD56 expression. *CIITA* truncating mutation may lead to loss of HLA-DR expression. Isochrome 7q and trisomy 8 here are not associated with hepatosplenic T-cell lymphoma. This presentation lacks more common recurrent mutations in ENKTL including those in the *JAK/STAT* pathway, *tp53* and *DDX3X*.

Panel Diagnosis: extranodal NK/T-cell lymphoma

Bilateral Adrenal Diffuse Large B-cell Lymphoma with Multisite Endocrine Involvement

Dr. Pallavi Khattar¹, Dr. Mona Sebika¹, Gervita Singh³, Dr. Susmitha Edappallath¹, PhD/MD Pratek Deb¹, Dr. Ram Singh², PhD/MD Wayne Tam¹

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Case Description

A 62-year-old woman presented with abdominal pain, early satiety, nausea, drenching night sweats, and 40-lb weight loss over four months. CBC was within normal limits; however, LDH was elevated (ranging from 158- 622 U/L). Ultrasound of the abdomen showed a poorly characterized left upper quadrant soft tissue density mass of 6.7 x 3.9 x 4.1 cm. PET-CT scan revealed bilateral adrenal masses (left 5.3x4.4 cm; right 4.2 x 3.0 cm); intensely FDG-avid (SUV max 49.6), and an enlarged thyroid gland with FDG-avid right thyroid lobe hypodensity measuring 2.9 x 2.8 cm, SUV 37.2. Endocrine evaluation demonstrated low cortisol without an increase in metanephrines or catecholamines. CT-guided adrenal biopsy (Bx#1) and subsequent thyroid biopsy (Bx#2) were performed. The patient was staged as IV-E bulky disease with B symptoms and started on R-CHOP, showing a marked metabolic response after three cycles.

Description of Submitted Tissues

Bx #1. CT-guided left adrenal gland core biopsy.

Bx #2. Ultrasound-guided right thyroid core biopsy and FNA.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded (FFPE) tissue; H&E and IHC performed on standard FFPE sections.

Frozen Tissue Available

No frozen tissue available.

Details of Microscopic Findings

Both adrenal and thyroid biopsies showed diffuse sheets of large atypical lymphoid cells with irregular nuclear contours, vesicular chromatin, prominent nucleoli, and abundant apoptosis. Brisk mitotic activity was present. Focal necrosis was noted in the thyroid sample.

Immunophenotype

Bx#1 (Adrenal Gland)

Neoplastic cells were positive for CD20, PAX5, CD79a, BCL6, BCL2, MUM1, MYC (40–50%), and variable p53; negative for CD3, CD5, CD10, Cyclin D1, CD21, CD23, CD30, and EBER. Ki-67 proliferation index: 80–90%.

Flow cytometry analysis detected a monotypic CD5-negative and CD10-negative B-cell population (24%).

Bx#2 (Thyroid Gland):

Neoplastic cells were positive for CD20, PAX5, BCL6, MUM1, MYC, BCL2, p53; while negative for CD3, CD5, CD10, cyclin D1, CD21, CD23, CD30, EBER. Ki-67 proliferation index is 90%.

Flow cytometry analysis detected a minute kappa-restricted B-cell population (1.7%) (similar immunophenotype as adrenal gland).

Cytogenetics

Bx#1 (Adrenal Gland)

FISH studies detected *BCL6* rearrangement (68%), *BCL2* deletion (46%), atypical, and no *MYC* or *BCL2* rearrangements.

Bx#2 (Thyroid Gland)

FISH studies detected *BCL6* rearrangement (76%), *BCL2* deletion (29.1%) atypical, and no *MYC* or *BCL2* rearrangements.

Molecular Studies

Bx#1 (Adrenal Gland)

NGS Lymphoid profile panel identified: *MYD88* S243N, *CD79B* Y196N, *CCND3* Q280*, *CDKN2A* R80*, *EBF1* C164Pfs*4, *MEF2B* E77K.

Proposed Diagnosis

Immune-privileged site–associated DLBCL involving bilateral adrenal glands with secondary thyroid involvement (Primary adrenal diffuse large B-cell lymphoma, with secondary thyroid involvement).

Interesting Feature(s)

This case shows simultaneous involvement of two immune-privileged endocrine organs, bilateral adrenal glands and thyroid gland, which is an uncommon presentation. The tumor harbors the characteristic molecular signature (*MYD88*/*CD79B* pathway mutations) of DLBCL of immune-privileged (IP) sites (WHO-HAEM5 classification) affecting the central nervous system, vitreoretinal tissues and testes. In addition, it shares the unique clinical feature of predilection for spread within immune- privileged sites of IP-DLBCL. This case highlights the clinicopathologic and genomic overlap between adrenal DLBCL and other IP site–associated DLBCL, underscoring its distinct biology and diagnostic importance, as well as supporting the inclusion of adrenal DLBCL in the category of WHO-defined IP-DLBCL.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-150

Primary ovarian large B-cell lymphoma of ABC and C5/MCD subtypes with systemic relapse.

Dr. Carmen Bárcena^{1,2}, Dr. Claire Royer¹, PhD/MD Bettina Bisig¹, Batiste Guey¹, Dr. Anne Cairoli¹, PhD/MD Laurence de Leval¹

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Case Description

A 68-year-old woman presented in June 2023, with fatigue, dyspnea and a 5kg loss. Her past medical history consisted of appendicectomy and endometriosis. A CT- scan revealed a 21.5 cm right ovarian mass. The patient underwent debulking cytoreductive surgery and was diagnosed with primary right ovarian diffuse large B- cell lymphoma, non- GC-like, ABC, stage IV, with massive infiltration of the right Fallopian tube and abdominal peritoneum. Numerous lymph nodes and left ovary without disease. She received R-CHOP (x6) + 2R, achieving complete remission in February 2025. In July 2025, she presented with an erythematous plaque on the right elbow. The skin biopsy was diagnosed with DLBCL, NOS, non-GC- like, ABC. One month later, a PET-CT scan revealed multifocal metabolic progression (lymph nodes, bone, soft tissues).

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

Yes.

Details of Microscopic Findings

Ovary: diffuse proliferation of large lymphoid cells with oval to round nuclei, fine chromatin, several nucleoli and moderate abundant cytoplasm. Numerous mitoses, apoptoses and necrosis were present.

Skin: dermal and hypodermal infiltration of a proliferation of large lymphoid cells.

Immunophenotype

Ovary: CD20+, CD5-, BCL2+, CD10-, BCL6+, MUM1+, MYC-, CD30-, p53wt, Ki-67 80%, EBER-.

Skin: CD20+, PAX5+, BCL2+, CD10-, BCL6+, MUM1+, MYC-, CD30-, Ki-67 90%.

Cytogenetics

FISH showed *BCL6* rearrangement, with no *MYC* or *BCL2* rearrangements.

Molecular Studies

- RT-MLPA (ovary and skin): ABC molecular subtype.
- NGS-based B-cell clonality (ovary and skin): identical clonotypes.
- NGS (228 genes):

- o Ovary:

- Mutations:

BTG2, *DTX1*, *DUSP2*, *IRF4*, *ITPK*, *PIM1*: several mutations, indicating aberrant somatic hypermutation.

Pathogenic mutation in *CD79B*.

Likely pathogenic mutations in *MYD88*, *BCL11B*, *ANKRD11*.

Genomic subtype: C5/MCD or ST2.

- o Skin:

- Mutations:

BTG2, *PIM1*, *SOCS1*: several mutations, indicating aberrant somatic hypermutation

Likely pathogenic mutations in *MYD88*, *BCL11B*, *ANKRD11*, *ETV6*.

Genomic subtype: C1/ST2.

Proposed Diagnosis

Diffuse large B-cell lymphoma, NOS

primary ovarian, with skin (and systemic relapse).

Interesting Feature(s)

- Primary ovarian lymphoma is rare. This case is a typical example of a primary ovarian large B-cell lymphoma, presenting as a large unilateral ovarian mass.
- The histogenesis of POL is unclear. It has been proposed that chronic inflammation involving the ovary in the setting of endometriosis, pelvic inflammatory disease or other inflammatory conditions may predispose to the development of NHL (PMID: 20668604), analogous to gastric MALT lymphoma. However, we did not find endometriosis in the surgical specimen.
- The overall genomic features in this case resemble those of lymphomas of immune-privileged sites, including concordant *MYD88* and *CD79B* mutations, footprints of aberrant somatic hypermutations, and *BCL6* rearrangement. However, the *MYD88* mutation was not the hotspot p.L265P variant.
- Comparative genomic study. The cutaneous relapse consisted of the same B-cell clone as the primary ovarian tumor. In addition to identical mutations in *CD79B*, *BCL11B*, *MYD88*, *ANKRD11*, numerous other mutations are present in only one or the other sample, reflecting ongoing somatic hypermutation. Using DLBCL genetic classification tools, the recurrence is classified differently from the tumor at the time of initial diagnosis (C5 at diagnosis, C1 at relapse, according to DLBclass; MCD or ST2 at diagnosis, ST2 at relapse, according to LymphGen).

Panel Diagnosis: DLBCL, NOS

Primary breast DLBCL initially presenting as CNS Lymphoma

Dr. Maria J. Tapken, Prof. Stefan Dirnhofer, Priv.-Doz. Jürgen Hench, Prof. Stephan Frank

University Hospital Basel, Institut für medizinische Genetik und Pathologie, Basel, Switzerland

Case Description

81-year-old resident of a nursing home with 10 days of increasing mental confusion. At clinical presentation she is hemodynamically stable, disoriented and shows signs of motor restlessness. CT-scan shows a hyperdense mass lesion of the Corpus callosum. Intraoperative biopsy reveals lymphoma on smear and histology, shallow nanopore sequencing epigenetically detects “Lymphoma / DLBCL” as well as an imbalanced copy number profile with potential LOH 6. Conventional methylation microarray-based classification confirms “Lymphoma / DLBCL” and the imbalanced copy number profile but remains without clear evidence for LOH 6 rendering “peripheral DLBCL” more likely than “PCNS-LBCL”. Staging CT showed a breast lesion; biopsy revealed DLBCL.

Biopsy Fixation Details

Fresh-frozen (brain) + formalin-fixed (4% buffered formalin) and paraffin-embedded (breast and brain)

Frozen Tissue Available

Yes

Details of Microscopic Findings

Brain: CNS tissue with a dense, structure-less infiltrate of medium- to large-sized cells with perivascular accentuation. Lesional cells show a high nuclear-to-cytoplasmic ratio, angulated, hyperchromatic, moderately pleomorphic nuclei, with inconspicuous nucleoli. Apoptosis is frequent.

Breast: Extensive necrosis adjacent to a monomorphic, dense infiltrate of medium- to large-sized cells. Lesional cells show a high nuclear-to-cytoplasmic ratio and angulated, hyperchromatic, moderately pleomorphic, with inconspicuous nucleoli. Only scattered lymphocytes and neutrophilic granulocytes are present. At the periphery of the lesion fibrosis, lymphocytes and histiocytes, but no preexisting breast parenchyma or other epithelial structures are perceptible

Immunophenotype

Breast: The lesional cells are CD20+B-cells with expression of BCL2, BCL6, cMYC (40-50 %) and MUM1. No expression of CD10, epithelial (CK22) or melanocytic markers. GATA3 stains tumour-infiltrating T-lymphocytes.

Brain: No evidence of EBV RNA (EBER1 and 2; ISH)

Cytogenetics

Breast: MYC-FISH (break-apart probe): No rearrangement detected

Molecular Studies

Brain:

Epigenome (**Nanopore and microarray**):

Methylation class Lymphoma / DLBCL

Copy number variation (**Nanopore**):

Imbalanced CNP, potential LOH 6

Copy number variation (**microarray**):

Imbalanced CNP, LOH 6 rather unlikely: Peripheral DLBCL more likely than PCNS-LBCL

Proposed Diagnosis

Primary diffuse large B-cell lymphoma (DLBCL), NOS, of the breast with CNS dissemination.

Non-GCB-Type (Hans-Algorithm)

Double Expressor Score: 2 (MYC+/BCL2+)

Interesting Feature(s)

• Supports the concept that primary extranodal DLBCL (breast, adrenal) might also belong to a/the specific subtype (immune-privileged sites), hence a potential extension to the WHO-entity of IP-DLBCL (testis, vitreoretina, CNS).

- DNA methylome together with copy number variation using Nanopore Sequencing enables reliable lymphoma diagnosis, much faster than FFPE, potentially more reliable than conventional fresh-frozen-section alone.
- DNA methylome alone does not unequivocally distinguish PCNS-LBCL from non-CNS LBCL (1).
- DNA methylome together with copy number variation could potentially distinguish PCNS-LBCL from non-CNS LBCL (2).
 - Liquid biopsy-based (lumbar puncture)!
 - Is a brain biopsy required?

1. Vogt J, Wagener R, Siebert R. Array-based profiling of the lymphoma cell DNA methylome does not unequivocally distinguish primary lymphomas of the central nervous system from non-CNS diffuse large B-cell lymphomas. *Genes Chromosomes Cancer*. 2019 Jan;58(1):66-69.
2. Hench J et al.; Rapid brain lymphoma diagnostics through nanopore sequencing of cytology-negative cerebrospinal fluid, *Acta Neuropathol*. 2024 Sep 3;148(1):36.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-188

Primary Large B-Cell Lymphoma of the Adrenal Glands (immune-privileged site) in a patient with Agent Orange Exposure

Dr. Zehra N. Kocas, Dr. Caitlyn Herrmann, Dr. Hariharan Bharadwaj

University of Massachusetts Chan Medical School - Baystate, Department of Pathology, Springfield, USA

Case Description

A 78-year-old man presented with abdominal pain, diarrhea, vomiting, generalized weakness, and B symptoms including unexplained weight loss. Past history included hypertension, hyperlipidemia, and CAD status post-CABG. Social history is notable for Agent Orange exposure during the Vietnam War and 60-pack-year smoking. Initial CT showed enlarged bilateral adrenal glands, concerning for bilateral adrenal hemorrhage. The patient was treated emergently for adrenal insufficiency/crisis and right renal artery embolectomy was performed. Three days later, MRI abdomen revealed bilateral adrenal masses (7.8 cm right, 9.5 cm left) without associated adenopathy. Radiologic differentials included lymphoma and metastatic carcinoma. Left adrenal biopsy was performed which established the diagnosis of primary adrenal diffuse large B-cell lymphoma. During hospitalization, the patient received R-CHOP chemotherapy, complicated by tumor lysis syndrome treated with rasburicase. He developed cytopenias requiring multiple transfusions and experienced severe hypotension from adrenal crisis versus septic shock; managed with vasopressors, stress-dose steroids and antibiotics. He improved with no infectious source found. The patient was ultimately discharged with an outpatient follow-up visit for the next chemotherapy cycle.

Biopsy Fixation Details

Specimen received in 10% neutral buffered formalin. Three tan-red soft tissue core biopsies ranging from 0.8 x 0.1 x 0.1 cm to 1.6 x 0.1 x 0.1 cm. Entirely submitted for histology.

Frozen Tissue Available

No frozen tissue available.

Details of Microscopic Findings

Core biopsies of the left adrenal gland showed sheets of large atypical lymphoid infiltrate with irregular nuclei, fine chromatin, variably prominent nucleoli and moderate amount of cytoplasm.

Immunophenotype

The neoplastic cells were CD20+ B-cells which co-expressed CD10, BCL6, MUM1, BCL2 (>95%) and weak CD5. CyclinD1, SOX11 and C-MYC were negative. Ki-67 proliferation index was 70–80%. CD21 highlighted no residual follicular dendritic cell meshwork. Scattered CD3+ CD5+ T-cells were present in the background. EBER in situ hybridization was negative.

Cytogenetics

FISH performed on paraffin-embedded tissue for MYC, BCL2, BCL6 and IRF4 gene rearrangements demonstrated a rearrangement involving the BCL6 gene only.

Molecular Studies

Molecular studies were not performed on this biopsy specimen.

Proposed Diagnosis

Primary Large B-Cell Lymphoma of the adrenal glands (immune-privileged site)

Interesting Feature(s)

Primary adrenal DLBCL is exceptionally rare and accounts for less than 1% of all lymphomas, with fewer than 300 reported cases.

The adrenal gland is considered an immune-privileged site due to its distinct biology compared with nodal DLBCL, including an NKT cell–enriched tumor microenvironment and clinical, pathologic, and genetic features similar to those of DLBCLs arising in classic immune-privileged sites (CNS and testes).

The patient's Agent Orange exposure suggests a possible environmental contribution to the pathogenesis of primary adrenal DLBCL; while Agent Orange has been linked to DLBCL, no published studies linking it specifically to immune-privileged or primary adrenal DLBCL.

The case is notable for the uncommon GCB subtype of primary adrenal DLBCL and an uncommon immunophenotype of GCB; showing co-expression of CD10, BCL6, and MUM1; necessitating exclusion of IRF4 rearrangement.

Clinically, primary adrenal DLBCL may cause adrenal insufficiency, highlighting the need for early recognition and consideration in adrenal mass evaluation.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-195

A case of donor-derived primary central nervous system peripheral T-cell lymphoma, not otherwise specified

Jingwei Li, David D. Grier, Robert B. Lersbach

Cincinnati Children's Hospital Medical Center, Division of Pathology and Laboratory Medicine, Cincinnati, USA

Case Description

A previously healthy 21-month-old male presented with fever and mild leukocytosis including 59% circulating blasts. A subsequent bone marrow evaluation demonstrated 94% T-lymphoblasts that expressed CD45, CD2, cytoplasmic CD3, surface CD3 (40% of blasts; weak), CD5, CD7, CD8, CD10, CD1a, TdT and CD4/CD8 coexpressed on ~25% of blasts, consistent with T-lymphoblastic leukemia (T-ALL). Karyotype evaluation demonstrated a clonal process with t(6;14)(q25;q11.2), suggestive of T-cell receptor locus (*TRA/TRD*) rearrangement. Staging cerebrospinal fluid cytology showed no evidence of central nervous system (CNS) involvement. He was initially treated with standard chemotherapy with bortezomib. His T-ALL relapsed at age 4, for which he was treated with standard chemotherapy with nelarabine and subsequently achieved minimal residual disease-negative clinical remission. He received a matched unrelated donor hematopoietic stem cell transplant (HSCT) at age 5 and remained healthy until age 8 when he presented with headache and left-sided weakness. Radiological study demonstrated multiple ill-defined

parenchyma brain lesions with midline shift and no evidence of disease outside of the CNS. A right frontal lobe brain lesion biopsy was subsequently obtained.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No

Details of Microscopic Findings

Sections show fragments of cellular tissue composed of small to medium sized cells arranged in sheets and perivascular aggregates with round to ovoid nuclei, irregular nuclear contours, coarse chromatin, inconspicuous to small nucleoli, and scant cytoplasm. Rare large and pleomorphic cells with irregular nuclear contours and occasional multilobated nuclei are also present.

Immunophenotype

The lesional cells are positive for CD3, CD7, CD30 (variable) and CD8. The lesional cells are negative for CD34, TdT, CD1a, CD10, CD20, PAX5, ALK-1, PD1, CXCL13 or ICOS. EBV EBER in-situ hybridization is negative.

Cytogenetics

Fluorescence in situ hybridization (FISH) studies demonstrated polyploidy in many of the probes tested and FISH XY study showed 83.8% female stem cell donor in a male stem cell recipient.

Molecular Studies

Next generation sequencing study showed pathogenic mutations involving *KRAS*, *TET2*, *CDKN2A/B*, *TP53* and *MSH6*.

Proposed Diagnosis

WHO 5th edition:

Peripheral T-cell lymphoma, NOS, EBV-, posttransplant setting (allogeneic HSC transplantation)

ICC 2022:

Monomorphic posttransplant lymphoproliferative disorder, peripheral T-cell lymphoma, NOS

Interesting Feature(s)

The patient's disease progressed despite therapy (dexamethasone, cytarabine, cisplatin) and he died of disease 4-month after diagnosis. T-cell posttransplant lymphoproliferative disorders (PTLDs) are rare, comprising approximately 2% of all PTLDs. Primary CNS T-cell lymphoma is rare in both immunocompetent and posttransplant patients with rare cases reported in the pediatric population. Mutations detected in this case are typical of PTCL-NOS, including *CDKN2A/B* deletion and *TP53* mutations. Donor-derived hematologic malignancies after HSCT are rare complications (159 reported cases since 1971). Reported donor-derived malignancies developed 0.8-26 years after HSCT (median: 2.2 years). Most common donor-derived hematopoietic malignancies are myelodysplastic syndrome and acute leukemias, while mature T-cell lymphomas are exceedingly rare. Mechanisms of donor-derived malignancy have been proposed, including premature aging of the donor's cells due to replicative effort to repopulate the donor's marrow and reduced immune surveillance because of the posttransplant immunocompromised state, among others.

Panel Diagnosis: IDD-LPD, PTCL NOS

Case Number: LYWS-208 Primary Large B-cell Lymphoma of the Meninges (Immune-Privileged Site) Presenting as Meningioma

Dr. Ali Y. Tug, Dr. AlBatool AlMahdy Abdelghaffar, Dr. Olga A. Krasnozhen-Ratush, Dr. Hariharan Bharadwaj

Baystate Medical Center, Pathology Department, Springfield, USA

Case Description

A 74-year-old male (history of HTN, hyperlipidemia, smoking) presented with progressive visual decline (May 2025) shortly after a fall with posterior occipital head trauma. Acute pathology was initially ruled out. By August 2025, vision deteriorated to light perception only. MRI revealed a 4.8 cm avidly enhancing, extra-axial mass centered in the left paraclinoid region, extending across the midline at the planum sphenoidale. Crucially, the lesion tracked along the left optic nerve sheath within the optic canal. Radiologic impression: en plaque meningioma. Preoperative high-dose methylprednisolone yielded subjective visual improvement. In October 2025, he underwent left pterional craniotomy. Due to high probability of meningioma, no frozen section was performed; gross total resection was pursued. Postoperatively, vision improved. Staging (CSF, marrow, PET/CT) was negative. Given the optic nerve sheath invasion, he was treated with CNS-penetrating High-Dose Methotrexate and Rituximab. He achieved complete remission; post-treatment imaging is normal.

Biopsy Fixation Details

Received in formalin: 4.9x2.4x1.3 cm aggregate. Sectioning showed tan-pink to red-white, soft, slightly friable tissue.

Frozen Tissue Available

None.

Details of Microscopic Findings

Dense, sclerotic connective tissue (dura) with focal cautery artifact, effaced by a diffuse infiltration of medium-to-large atypical lymphoid cells. Neoplastic cells exhibit moderate-to-abundant cytoplasm, open chromatin, and irregular nuclear contours. High cellularity areas show frequent apoptotic bodies.

Immunophenotype

Neoplastic B-cells (CD20+, PAX5+) with GCB phenotype: BCL6+, CD10-, MUM1-. Notably, tumor cells show aberrant, strong membranous co-expression of CD21 and CD30 (~80%); CD21 outlines tumor cells. Negative: CD5, BCL2, CD23, Cyclin D1, ALK, EBER, C-MYC. Ki-67 ~30% (discordant with morphology).

Cytogenetics

FISH testing: *BCL6* translocation (3q27) and *BCL2* copy number gain (3 copies). No *MYC* rearrangement.

Molecular Studies

No Lymphoma NGS. Marrow Myeloid NGS: *DNMT3A* Q534* mutation (VAF 15%), consistent with CHIP, and *BCOR* p.T936N variant (germline polymorphism).

Proposed Diagnosis

Primary Dural-Based Diffuse Large B-Cell Lymphoma (DLBCL), NOS, GCB-type (Primary Large B-cell Lymphoma of Immune-Privileged Sites)

Interesting Feature(s)

Mimicry: Primary Dural Lymphoma is rare (<1% CNS lymphomas), but DLBCL accounts for ~50% of cases and mimics meningioma radiologically in >90%. High probability precluded frozen section; had it been performed, management might have shifted to tissue-sparing surgery. Rapid progression was a red flag distinguishing high-grade malignancy from indolent meningioma.

Discordant Grade: DLBCL diagnosis contrasts with low Ki-67 (~30%). DLBCL favored due to morphology, apoptosis, and aggression. "Proliferative discordance" is likely an artifact of preoperative corticosteroids inducing cell cycle arrest and lymphocytolysis.

Trauma-Associated "Contrecoup": Tumor arose at the anterior planum sphenoidale shortly after posterior occipital impact. Theories: 1) Tumorigenesis via chronic inflammation; 2) Seeding of circulating cells. Short latency suggests the injury served as a nidus.

Prognosis: Favorable indicators despite high grade: Aberrant co-expression of CD21 (normally lost in DLBCL) and CD30 in a MYC-negative GCB-type lymphoma is associated with better survival overall.

Treatment: While dural lymphomas are often treated like systemic disease (outside BBB), optic nerve sheath invasion placed this within a CNS sanctuary site. This necessitated High-Dose Methotrexate to penetrate the blood-optic nerve barrier, ensuring remission.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-209

Primary testicular B-lymphoblastic lymphoma with novel *PAX5::BPIFB2* fusion

Jingwei Li, David D. Grier, Robert B. Lersbach

Cincinnati Children's Hospital Medical Center, Division of Pathology and Laboratory Medicine, Cincinnati, USA

Case Description

A previously healthy 13-year-old male presented with a 1 month history of painless swelling of the right testis without recent history of testicular trauma, fevers, weight loss, night sweats or lymphadenopathy. Testicular ultrasound identified a large hypoechoic mass replacing most of the right testicular parenchyma. Given the high clinical and radiological suspicions for a neoplastic process, the patient subsequently underwent right orchiectomy. A fluorodeoxyglucose positron emission tomography (PET) study revealed single PET-avid (Standardized Uptake Value: 11.3) pericaval lymph node which was difficult to definitively visualize due to the adjacent inferior vena cava. Otherwise, there were no other lesions suspicious for lymphoma involvement identified radiologically or clinically. A staging bone marrow evaluation showed no evidence of malignancy.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No

Details of Microscopic Findings

Microscopic examination of the tissue section showed effacement of the normal testicular tissue. Most of the tissue consists of intermediate sized, atypical lymphoid cells with open chromatin, irregular nuclear contours, prominent nucleoli, and scant cytoplasm.

Immunophenotype

The lesional cells are strongly positive for TdT and PAX5 negative for CD15, myeloperoxidase or CD3. Scattered residual seminiferous tubules are present in the background. Flow cytometry performed on the lesional tissue sample reveals a population of B-lymphoblasts (95.5% of all cells) that express CD19, partial CD20 (approximately 15% of all blasts), CD10, HLA-DR, CD34, and partial CD15 (approximately 14%). The cells are negative for CD5, CD23, kappa and lambda surface immunoglobulin light chains, CD30 or other markers tested.

Cytogenetics

Not performed

Molecular Studies

Next generation sequencing (NGS) study demonstrated a *PAX5::BPIFB2* fusion, a *FLT3* Internal tandem duplication (ITD), *IKZF1* homozygous loss, and segmental loss of chromosome 9p including *CDKN2A/B*, among other copy number variations.

Proposed Diagnosis

WHO, 5th edition:

B-lymphoblastic lymphoma with *PAX5* alteration (testicular primary)

ICC:

B-lymphoblastic lymphoma, *PAX5* altered (testicular primary)

Interesting Feature(s)

Primary testicular lymphomas occur predominantly in older adult males with a median age of 67-years at diagnosis) and are the most common primary testicular malignancy in this age group which consist mainly of diffuse large B-cell lymphoma. Primary testicular lymphoma, including testicular follicular lymphoma, is uncommon in children. Only rare patients with primary testicular B- or T-lymphoblastic lymphoma have been reported. By 2023, only eight primary testicular B-lymphoblastic lymphoma cases were reported in the literature.

Primary lymphomas of immune-privileged sites arise, in part, because of genetic alterations that affect the tumor microenvironment and recognition of lymphoma cells by the immune system, including copy number gains of 9p24.1 (CD274, *PD-L1*) and loss of class I and II gene loci; such alterations are lacking in the current case. A novel *PAX5::BPIFB2* fusion was detected by NGS in this case. BPIFB2 is mainly expressed in oral epithelium, salivary gland, skin, tonsil and are not expressed in hematolymphoid cells. Given the preserved paired box domain, PAX5 fusion proteins retain DNA bindings and are thought to inhibit PAX5 through a dominant-negative mechanism. *FLT3*-ITDs are rarely seen in childhood B-lymphoblastic leukemia (2.5%) and may identify a novel B-ALL/LBL subgroup with targetable therapy options.

Panel Diagnosis: B-LBL

EA4HP26-LYWS-224

Bilateral primary Adrenal Diffuse large B cell lymphoma

Prof. Tanuja Shet¹, Dr. Sridhar Epari², Dr. Rutvij Khedkar¹

¹ Tata Memorial Hospital, Pathology, Mumbai, India; ² ACTREC, Pathology, Kharghar, India

Case Description

61 year old male known hypertensive came in 15th July 2024 with Pain in abdomen since 21 days. He had fever but no loss of weight and night sweats

His serum biochemistry including renal function test revealed no abnormality

Hb – 10.2g/DL, with hypochromic microcytic anemia. Peripheral blood MDC was normal

His USG abdomen revealed bilateral suprarenal masses following which a PET scan was done.

There were no signs of adrenal insufficiency. Serum cortisol was 12.7 ng/dL (normal value 2.47-11.9 ng/dL done on cobas e801)

Under the impression of pheochromocytoma patient U/w left adrenalectomy at outside hospital (01/07/24)

Following a diagnosis of Diffuse large B cell lymphoma patient was scheduled for 6# RCHOP WITH GCSF SUPPORT + IT MTX WITH 2 # HDMTX

Patient took 4# CHOP but had severe neutropenia and lung infections

With delay in chemotherapy patient had disease progression

Patient succumbed on 2 Jan 2025

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

No

Details of Microscopic Findings

Gross :- Received left adrenal mass measuring 12X10X7 cm weighing 262gms. Capsulated with minimal fascia and fat covering half of surface. Cut surface showed circumscribed lobulated tan colored tumor.

Histology : revealed a tumor with diffuse sheets of large cells with centroblastic morphology and patchy hemorrhage and necrosis

Scanty preserved adrenal gland was seen at periphery of the tumor.

Immunophenotype

- Positive : CD20, bcl2 , bcl6,
- Negative : CD3, Cd10, MUM1, EBERISH
- Cmyc 20%

Cytogenetics

Nil

Molecular Studies

NGS awaited

Proposed Diagnosis

Bilateral primary adrenal diffuse large B cell lymphoma non GCB type

Interesting Feature(s)

- Rare case of primary adrenal DLBCL
- Normal adrenal cortical function
- Aggressive course as compared to other organs

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-234

EBV-positive NK/T-cell lymphoma of the testis

Dr. Judit Bedekovics¹, Dr. Edit Páyer², Dr. Anikó Ujfalusi³, Krisztina A. Chalupa¹, Prof. Gábor Méhes¹

¹ University of Debrecen, Department of Pathology, Debrecen, Hungary; ² University of Debrecen, Department of Internal Medicine, Debrecen, Hungary; ³ University of Debrecen, Clinical Genetics Centre, Debrecen, Hungary

Case Description

49-year-old male patient was admitted with painless enlargement of the right testis. A scrotal ultrasound (US) revealed a 45 x 44 x 28 mm, inhomogeneous mass in the right testis. Consequently, a high radical orchidectomy was performed, and histopathology identified NK/T-cell lymphoma.

Chest, abdominal, and pelvic CT scans showed no evidence of malignant dissemination. PET/CT scan identified hypermetabolic cutaneous lesions on the left thigh and right upper arm. SUVmax value of 10.8 and 4.6 respectively). A core biopsy of the PET/CT-positive lesion on the left thigh confirmed the presence of NK/T-cell lymphoma. Bone marrow biopsy and bone marrow aspiration was performed. Bone marrow trephine biopsy was negative for T-cell lymphoma. In the bone marrow aspirate, 8.0% of the cells were T-cells (CD4/CD8 ratio: 0.64) and 1.8% were NK cells. The T-cell receptor (TCR) chain ratio was 9.8, which was not suggestive of monoclonal T-cell proliferation. Blood test for EBV PCR was positive.

The patient received treatment according to the SMILE protocol, followed by an autologous bone marrow transplantation. Prophylactic radiotherapy of the contralateral testis was also performed. Ten months have passed since the bone marrow transplantation. The patient is currently asymptomatic, and the follow-up PET/CT scan shows Complete Metabolic Remission (CMR).

Biopsy Fixation Details

10% Neutral Buffered Formalin is used, with a fixation time of 8-24 hours.

Frozen Tissue Available

No.

Details of Microscopic Findings

Within the testicular parenchyma, proliferation of atypical cells was identified with a diffuse growth pattern. The infiltration partially destroyed the testicular architecture, and the atypical cells surrounded and partially infiltrated the testicular tubules. The cells exhibited a pleomorphic appearance with varied nuclear shapes; nuclear indentations were noted, clear cytological atypia was present, and nucleoli were identifiable. Scattered eosinophil granulocytes were present. Mitotic index: 53/10 HPF, Mib-1 labeling index: >90%.

Immunophenotype

Immunohistochemical staining revealed the following immunophenotype: CD3+, CD43+, CD2+, CD5-, CD7-, CD4-/+, CD8-, CD56-, Granzyme B diffuse+, TIA-1 diffuse+, TdT-, CD20-, PAX5-, CD10-, BCL6-, PD1-, with 1% CD30 expression.

Cytogenetics

Not applicable.

Molecular Studies

NGS analysis of bone marrow aspirate detected *TET2* mutation c.1630C>T (p.Arg544*) with 4.03% VAF. EBER in situ hybridisation was positive confirming the presence of EBV.

Proposed Diagnosis

Extranodal NK/T-cell lymphoma (non-nasal).

Interesting Feature(s)

Non-nasal subtype of extranodal NK/T-cell lymphoma account for 20% of cases, Although the testis is a typical site for extranodal NK/T-cell lymphoma, it is a rare subtype of primary testicular lymphomas. The detection of a *TET2* mutation in the bone marrow is suggestive of clonal hematopoiesis.

Panel Diagnosis: extranodal NK/T-cell lymphoma

EA4HP26-LYWS-248**Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with prominent plasma cell differentiation of the cranial dura: a case report**

Dr. Maria-Alexandra Matanie¹, Dr. Hippolyte Lecureur², Dr. Radu Pirlog¹, Cyrielle Robe¹, Dr. Josette Brière¹, Prof. Emmanuèle Lechapt-Zalcman¹, Prof. Philippe Gaulard¹, Dr. Elsa Poullot¹

¹ Henri Mondor University Hospital, Pathology, Creteil, France; ² Foch Hospital, Pathology, Suresnes, France

Case Description

A 34-year-old man with no significant past medical history was admitted in April 2024 for new-onset epileptic seizures. Brain MRI revealed a bilateral frontal mass, predominantly on the left, with associated perilesional edema, suggestive of a dural-based expansive lesion adjacent to the falx cerebri, compatible with a meningioma. Antiepileptic therapy was initiated. In June 2025, he experienced two additional epileptic seizures, complicated by a right shoulder fracture-dislocation. In September 2025, the lesion was surgically resected (slides submitted).

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The dural fragments demonstrate a diffuse lymphoid infiltrate. Atrophic lymphoid follicles are present, surrounded by a prominent infiltrate showing marked plasmacytic differentiation, with plasma cells exhibiting eccentrically located nuclei with mottled (“clock-face”) chromatin and abundant eosinophilic cytoplasm. No areas of necrosis are identified.

Immunophenotype

The lymphomatous areas are diffusely CD79A+, and partially CD20+ (follicular areas). The plasma cell component is CD138+, MUM1+, CD56-, cyclin D1-, c-KIT-, IgG+, IgG4-, IgM- and shows kappa light chain restriction. A follicular dendritic cell meshwork highlighted by CD21 and CD23 underlies the residual follicles. The Ki-67 rate is weak (5%).

Cytogenetics

NA

Molecular Studies

Targeted Gene Sequencing (36 genes panel dedicated to B cell lymphoma) : pathogenic mutation detected of *NOTCH1* (p.A1927P, VAF 14.8%) and *PIM1* (p.S77N, VAF 13%). No *MYD88* or *CXCR4* mutations are identified.

Proposed Diagnosis

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with prominent plasma cell differentiation of the cranial dura.

Interesting Feature(s)

- Rare entity (approximately 120–140 cases reported in the literature worldwide), with a dedicated chapter in the Central Nervous System Tumours WHO classification (5th Edition).
- Typically arises in the cranial dura mimicking meningiomas or, less commonly, subdural hematomas.
- Indolent and associated with an excellent prognosis.
- In our case : Prominent plasma cell differentiation with diagnostic challenge between this entity, plasma cell neoplasms (plasmacytoma or multiple myeloma) or lymphoplasmacytic lymphoma.

Panel Diagnosis: extranodal MZL

EA4HP26-LYWS-250

EBV-positive extranodal NK/T-cell lymphoma presenting as uveitis and bilateral adrenal masses

Dr. Alexa Andre¹, Dr. Lianqun Qui², Dr. Kenn Chen¹, Dr. Kikkeri Naresh³, Dr. Xueyan Chen³, Dr. Jason Love¹

¹ University of Washington, Department of Laboratory Medicine and Pathology, Seattle, USA; ² MD Anderson, Department of Pathology, Dallas, USA; ³ Fred Hutchinson Cancer Research Center, Department of Pathology, Seattle, USA

Case Description

- 39-year-old male from Mexico initially presented with right eye pain
- He was diagnosed with uveitis, worrisome for tuberculous uveitis and underwent vitrectomy
- Vitreous fluid cytology showed scattered atypical cells and flow cytometry demonstrated an abnormal population of large lymphocytes expressing CD2, CD38, CD45, and CD56 with no surface CD3, CD4, CD5, CD7, CD8 or CD30
- During work-up, the patient was admitted for progressive dyspnea, cough, night sweats, and intermittent fever
- CT abdomen pelvis showed bilateral adrenal masses (7.1 cm and 4.8 cm) and ultrasound demonstrated bilateral testicular enlargement. An adrenal mass was biopsied.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No frozen tissue

Details of Microscopic Findings

H&E stained slides show adrenal gland with a dense and diffuse infiltrate of atypical lymphocytes

Sheets of atypical medium to large sized cells are present with irregular nuclear contours, coarse chromatin, occasional small distinct nucleoli and variable amounts of clear or vacuolated cytoplasm

Mitotic activity is brisk and apoptotic bodies are abundant.

Immunophenotype

Positive:

- CD2
- CD3 (cytoplasmic)
- CD56
- BCL2 (major subset)
- TIA1
- Granzyme B
- EBER in situ hybridization
- 90% Ki-67 proliferative rate

Negative:

- CD5
- CD8
- CD20
- CD30
- BCL6
- T-cell receptor beta F1 and T-cell receptor delta
- Negative for tested Kir antigens

Cytogenetics

Normal 46, XY

Molecular Studies

None

Proposed Diagnosis**EBV-positive extranodal NK/T-cell lymphoma**

- Presenting with ocular and bilateral adrenal gland involvement
- Bilateral testicular enlargement was present at presentation but not biopsied
- Subsequent biopsies demonstrated occult NK/T cell lymphoma in the nasal sinuses
- Disease was also found in the CSF and blood using flow cytometry

Interesting Feature(s)

Initial presentation of ENKTL with ocular symptoms and bilateral adrenal masses is rare

- In one series, 12 of 103 cases of NK/T cell lymphoma showed proven ocular involvement, and only one patient presented with eye symptoms
- Only 8 cases of primary adrenal extranodal NK /T cell lymphoma have been reported in the literature
- This case demonstrates that ENKTL can present with prominent involvement of immune-privileged sites
- Nasal presentation of extranodal NK/T cell lymphoma accounts for about 80% of cases
- If occult nasal involvement is found on clinical investigation, should be reclassified as advanced nasal-subtype ENKTL instead of de novo non-nasal ENKTL
- Our patient had occult involvement of the ethmoid and maxillary sinuses and using the above criteria would be best reclassified and treated as advanced nasal-subtype of ENKTL

EA4HP26-LYWS-258

Diffuse large B-cell lymphoma of the CNS involving the nasopharynx

Dr. Reenal Patel, Dr. Sarang Khan, Dr. Olabisi Afolayan-Oloye

Corewell Health East William Beaumont University Hospital, Hematopathology, Royal Oak, USA

Case Description

75-year-old man with prior non-muscle invasive bladder cancer and TAVR presented with 3 weeks of diplopia and right ptosis. Brain MRI showed an infiltrative skull-base mass involving the clivus, sella, sphenoid, right cavernous sinus, nasopharynx, choana, and posterior septum. Debulking revealed a bone-eroding tumor extending into the nasal cavity, invading the septum, clivus, and choanal arch.

Biopsy Fixation Details

Formalin-fixed Paraffin embedded.

Frozen Tissue Available

Frozen section suggested lymphoma; workup initiated.

Details of Microscopic Findings

H&E showed sheets of large atypical B cells with vesicular nuclei, prominent nucleoli, frequent mitoses, apoptosis, and geographic necrosis.

Immunophenotype

Flow cytometry showed a CD5–/CD10– kappa-restricted B-cell population (~19%). IHC revealed large B cells positive for CD20, PAX5, BCL6, MUM1, BCL2, CD30 with high Ki-67 (80–90%), and negative for CD5, CD10, cyclin D1, MYC, CD23, and EBER.

POSITIVE MARKERS	NEGATIVE MARKERS
CD20	CD3
PAX5	CD5
BCL6	CD10
MUM1 (>30%)	BCL1
BCL2 (>50%)	cMYC (<40%)
CD30	CD21/ CD23
Ki67 - 80-90%	EBER

Cytogenetics

FISH showed MYC gain (3 copies) in ~57% of nuclei without MYC or IGH::MYC rearrangement, excluding double-hit lymphoma.

Molecular Studies

None

Proposed Diagnosis

Diffuse large B-cell lymphoma (DLBCL), non-germinal center B-cell subtype by Han's algorithm, negative for MYC gene rearrangement; negative for double-hit lymphoma.

Interesting Feature(s)

One of a kind case originating from the skull base and associated sinonasal presentation, clinically mimicking an aggressive infiltrative epithelial or skull base tumor. This case was a non-germinal center B-cell phenotype by Hans algorithm, a subtype associated with poorer prognosis and distinct biology. Notably, instead of a MYC rearrangement, only MYC amplification was identified, highlighting a rare genetic alteration with potential pathogenetic and prognostic implications. The combination of atypical anatomic location, non-GC immunophenotype, and isolated MYC amplification makes this case diagnostically and biologically distinctive.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-259

Primary Ovarian Lymphoma Mimicking Sex Cord Stromal Tumor

Dr. Cody Forsyth, Dr. Giovanni Botten, **Prof. Sheeja Pullarkat**

UCLA David Geffen School of Medicine, Hematopathology/ Pathology and Laboratory Medicine/ UCLA, David Geffen School of Medicine, Los Angeles, USA

Case Description

- 48-year-old female with past medical history of primary cutaneous follicle centre lymphoma (PCFCL) of the scalp treated with excision and complicated by local recurrence, who presented for evaluation of abnormal uterine bleeding.
- MR pelvis demonstrates 4.7 cms enhancing right adnexal mass with diffusion restriction, concerning for solid ovarian neoplasm or sex cord stromal tumor.
- Endometrial biopsy showed benign endocervix with no endometrium present for evaluation.
- Subsequently presented for right salpingo-oophorectomy with endometrial curettage.
- Imaging studies showed no lymphadenopathy, negative for hepatosplenomegaly, and no other sites of involvement

Biopsy Fixation Details

Tissue specimen fixed in 10% neutral buffered formalin (NBF) with a minimum tissue-to-formalin ratio of 1:5 for up to 24 hours.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Microscopic sections revealed large, highly atypical mononuclear cells invading the ovarian parenchyma in a nodular and diffuse pattern. The cells had a high nuclear-to-cytoplasmic ratio, irregular nuclear contours, and prominent nucleoli, resembling centroblasts. In the nodular areas, the centroblasts were >15 HPF and formed clusters without intervening centrocytes. In some areas, the nodular architecture was lost, and sheets of large cells were noted (diffuse areas). Increased mitotic activity was noted. No areas of necrosis were identified,

Immunophenotype

Immunohistochemical studies showed positivity for CD19, CD20, PAX5, BCL2, BCL6, and lambda light chain, with a Ki67 proliferation index of >80%.

The neoplastic cells are negative for CD10, MUM1, cMYC, BCL1, and Epstein-Barr virus (EBV)-encoded RNA (EBER) in situ hybridization.

Cytogenetics

Fluorescence in situ hybridization (FISH) analyses performed for following probes:•BCL6 dual-color, break apart (3q27)

- MYC dual-color, break apart (8q24)

- IGH::MYC dual-color, dual-fusion t(8q24;14q32)
- IGH::BCL2 dual-color, dual-fusion t(14q32;18q21)

FISH Results Summary:

+3q (observed in 12.5% nuclei)

+8q (observed in ~11.5-13.5% nuclei)

Negative for t(8;14)

Negative for t(14;18)

Negative for BCL6 rearrangements Negative for MYC rearrangements

Molecular Studies

Not performed

Proposed Diagnosis

Follicular Large B-cell Lymphoma (formerly FL Grade 3B) with areas of Diffuse Large B-cell Lymphoma (WHO 5th)

Interesting Feature(s)

- Primary ovarian lymphomas are an important differential diagnosis to consider in the workup of adnexal masses. The treatment of lymphoma involves chemotherapy as opposed to surgical resection, which is the treatment approach for other primary ovarian neoplasms. Therefore, accurate and timely diagnosis is important for initiating appropriate therapy.
- Ovarian lymphomas are rare accounting for <1% of ovarian malignancies•Canonical driver rearrangements like t(8;14) and/or t(14;18) are relatively uncommon in Lymphomas of immunoprivileged sites
- Copy number alterations in BCL6 are commonly seen, as evidenced in our case
- This patient has a previous history of primary cutaneous follicle centre lymphoma (PCFCL) of the scalp. However, because the imaging studies showed no additional sites of involvement, we believe that the current case represents primary lymphoma of the Ovary.Follow-up: The patient was treated with 4 cycles of RCHOP and is disease-free 3 years after the initial diagnosis

Panel Diagnosis: FL3B/DLBCL

EA4HP26-LYWS-260

Immune privileged site lymphoma of the meninges

Núria Vidal-Robau, Melina Pol, Gerard Frigola, Elías Campo, Olga Balague

Hospital Clinic Barcelona, Pathology Department/Hematopathology Section, Barcelona, Spain

Case Description

A 91-year-old woman with medical history of breast cancer resected over 20 years ago and a recent transient ischemic attack presenting as aphasia, developed cauda equina syndrome. Lumbar MRI revealed an anterior **epidural solid mass** with contrast enhancement extending from the upper L3 to the lower L5 levels, as well as additional ill-defined foci of contrast enhancement including the distal conus medullaris and the distal filum terminale. A biopsy of the epidural mass confirmed **diffuse large B-cell lymphoma**. Staging thoracoabdominal CT demonstrated multiple hepatic lesions in the right lobe (maximum 4.7 cm), bilateral adrenal masses and renal focal lesions, and retroperitoneal lymphadenopathy at the celiac, bilateral renal hilar, and interaortocaval region, which were never biopsied although they were suggestive of solid metastatic disease. Palliative management was chosen without further diagnostic procedures, and the patient subsequently died.

Biopsy Fixation Details

Formalin-Fixed Paraffin-Embedded

Frozen Tissue Available

Yes, OCT

Details of Microscopic Findings

Fibrous tissue fragments with diffuse infiltration by large cells, with poorly defined cytoplasm, large irregular nuclei with vesicular chromatin, and some with multiple nucleoli; few small accompanying lymphocytes are present.

Immunophenotype

Immunohistochemical studies show that neoplastic cells are positive for CD20, PAX5, BCL2, and MUM1. MYC is weakly positive in less than 50% of neoplastic cells, and P53 is positive in approximately 25%. The cells are negative for CD10, BCL6, CD3, CD5, and TDT. CD21 and CD23 staining does not reveal a follicular dendritic cell meshwork. The proliferative index (Ki67) is 80%. In situ hybridization for Epstein-Barr virus (EBER) and Human Herpesvirus 8 are negative.

Cytogenetics

FISH

-*BCL6*: not assessable

-*BCL2* and *MYC*: normal

Molecular Studies

Lymph2Cx: ABC

Proposed Diagnosis

Diffuse Large B Cell Lymphoma (DLBCL), ABC type

Interesting Feature(s)

This is a DLBCL localized in the meninges. It could be considered a primary meningeal lymphoma, although the presence of lesions suggestive of M1 involvement (not biopsied) may challenge this diagnosis.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-264

Aggressive NK cell lymphoma involving the CNS with associated hemophagocytic lymphohistiocytosis

Dr. Stephen J. Babcock¹, Dr. Sarah Nikiforow², Dr. Sarah J. Wu¹

¹ Brigham and Women's Hospital, Pathology, Boston, USA; ² Dana Farber Cancer Institute, Medical Oncology, Boston, USA

Case Description

A 56-year-old male presented with dyspnea, bloody sputum, and fever. He was found to have altered mental status (AMS), pancytopenia, and fever which persisted despite broad antibiotics and negative cultures. Splenomegaly and hyperferritinemia were also noted.

Hemophagocytic lymphohistiocytosis (HLH) was suspected, and bone marrow biopsy was performed, demonstrating hemophagocytosis without evidence of a hematologic neoplasm. CXCL9 and sCD25 were elevated, consistent with HLH. PET-CT did not show definitive lesions, and peripheral blood flow cytometry did not demonstrate a T or B lymphoproliferative disorder.

The patient was treated for idiopathic HLH on the HLH-94 protocol (etoposide, steroids). He initially improved, but suffered two recurrences over 4 months. On his second recurrence, AMS prompted lumbar puncture, which showed elevated nucleated cells and protein. Repeat marrow and CSF studies were performed. During work-up, the patient expired and autopsy was requested.

Biopsy Fixation Details

A cell block was created by plasma thrombin technique, then fixed in formalin. The brain was fixed in formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

Cytopathologic evaluation of the CSF specimen showed numerous atypical medium-to-large mononuclear cells with irregular nuclei, fine chromatin, small to prominent nucleoli, and moderate-to-large amounts of pale cytoplasm with coarse azurophilic cytoplasmic granules. Frequent atypical mitotic figures were seen. Background histiocytes exhibited phagocytosis of intact nucleated cells.

Concurrent flow cytometry of the CSF showed an NK cell immunophenotype with aberrant loss of CD7. A bone marrow biopsy was inadequate for evaluation of marrow elements but flow cytometry detected a minute population of NK cells with the same immunophenotype as well as an expanded population of gamma-delta T cells.

Following the patient's expiry, an autopsy was requested by the family. Examination of the brain showed leptomeningeal involvement of the cerebellum by atypical NK cells, which were positive for CD2 and negative for EBER.

Immunophenotype

IHC: CD2+ CD56+ TIA1+ Perforin+ Granzyme+ CD30+ CD3- CD5- CD7- TCRδ- TCRγ- TCRBF1- EBER-
Flow: CD2+ CD56+ CD45+ CD16+ CD11c+ CD38+ CD3- CD5- CD7- CD4- CD8- CD57-

Cytogenetics

Cytogenetics performed on bone marrow were limited by a paucity of metaphases. 46,XY[5]

Molecular Studies

Next-generation sequencing performed on bone marrow identified mutations in *STAT3* and *TP53*. T-cell receptor clonality studies performed on the cell block showed a polyclonal pattern.

Proposed Diagnosis

EBV-negative Aggressive Natural Killer Cell Leukemia/Lymphoma of the central nervous system with secondary (malignancy-associated) Hemophagocytic Lymphohistiocytosis

Interesting Feature(s)

This case highlights the challenge of finding the primary malignancy in malignancy-associated secondary HLH. In practice, many 'idiopathic' cases of HLH may be due to occult infection, occult malignancy, or rarely to late onset primary HLH. When infection has been clinically excluded and suspicion for late onset primary HLH is low, an exhaustive search for a malignancy is required to exclude malignancy-associated HLH. In cases where a primary malignancy is not readily identified by imaging and peripheral blood studies, the central nervous system may act as a sanctuary space where malignant cells are difficult to identify on imaging and are shielded from systemic therapies, as in this case. This also represents a case of EBV-negative aggressive NK cell leukemia/lymphoma, a neoplasm associated with EBV infection in ~90% of cases.

Panel Diagnosis: extranodal NK/T-cell lymphoma

EA4HP26-LYWS-274

High-grade B-cell lymphoma presenting as bilateral adrenal lesions in a post-solid-organ transplantation setting

Dr. William Wu¹, Dr. David Gajzer¹, Dr. Christopher Snyder¹, Prof. Kikkeri Naresh¹, Dr. Jason Love¹

¹ University of Washington, Department of Laboratory Medicine and Pathology, Seattle, USA; ² Fred Hutchinson Cancer Center, Seattle, USA

Case Description

A 59-year-old male with history of orthotopic liver transplant (2012) for hepatitis C-related cirrhosis with confirmed HCV clearance, on stable tacrolimus and mycophenolate mofetil regimen, presented to the emergency department in 2021 for acute onset abdominal pain. CT imaging revealed bilateral adrenal masses measuring up to 5.9 cm (left) and 4.4 cm (right) in greatest dimension. Plasma metanephrine and normetanephrine levels were normal.

Evaluation was otherwise non-diagnostic for a specific acute pathology.

Follow-up MRI showed central necrosis within the adrenal masses; subsequent CT 7 weeks after initial presentation showed interval growth of both masses to 6.6 cm (left) and 5.3 cm (right). The right adrenal mass was biopsied.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Histologic sections showed core biopsy material of adrenal gland with diffuse infiltration by sheets of predominantly medium to large atypical lymphoid cells with irregular nuclear contours, vesicular chromatin, conspicuous nucleoli, and a moderate amount of cytoplasm. Mitotic activity was brisk and apoptotic bodies were frequent. Focal necrosis was seen.

By IHC, the atypical lymphoid cells were positive for CD20, BCL-2 (diffuse), CD10 (diffuse), BCL-6 (diffuse), c-MYC (60%), and CD19 (diffuse), and negative for MUM-1 (< 30%), cyclin D1, and TdT. EBER was negative by in situ hybridization (ISH). Ki-67 proliferative index was >95%. CD3 highlighted T cells.

Immunophenotype

Flow cytometry: The abnormal mature B cell population identified by flow cytometry represented 81% of total white cells and showed increased forward and side scatter properties. The population expressed CD10, CD38, CD45, BCL-2, CD19, and CD20 with lambda light chain restriction. There was no expression of CD5 or TdT.

Summary:

Positive: CD19, CD20, CD10, BCL-6, BCL-2, c-MYC, >95% Ki-67 index

Negative: EBER ISH, MUM-1, TdT

Cytogenetics

FISH performed on FFPE tissue:

- Positive for rearrangement of 8q24.1 involving *MYC* in 89% of cells (3.9% cutoff)
- Negative for rearrangement of 3q27 involving *BCL6* (6.2% cutoff)
- Negative for rearrangement of 18q21 involving *BCL2* (3.0% cutoff)

ISCN: nuc ish(BCL6x2)[200],(MYCx2)(3'MYC sep 5'MYCx1)[177/200],(BCL2x2)[200]

MYC::IGH studies are ongoing.

Molecular Studies

N/A

Proposed Diagnosis

High-grade B-cell lymphoma, EBV-negative, post-transplant setting.

MYC rearrangement is positive. The main differential diagnoses include diffuse large B-cell lymphoma and high-grade B-cell lymphoma, NOS. Given the medium size of the cells, very high Ki-67 proliferative index and lack of significant pleomorphism, the diagnosis of high-grade B-cell lymphoma, NOS, is favored. The overall cytologic features and strong BCL-2 expression of the lymphoma cells are not consistent with Burkitt lymphoma. Given the history of liver transplant, the diagnosis is specified as a lymphoma arising in immune deficiency/dysregulation (IDD-lymphoma), post-transplant setting.

Interesting Feature(s)

Our case shows that IDD-lymphomas can manifest as primary adrenal masses.

Some studies have raised the possibility of the adrenal gland being a site of immune privilege associated with an immunosuppressive microenvironment.

Primary post-transplant IDD-lymphoma of the adrenal is extremely rare. Reported cases have been unilateral and EBV-positive. This case features bilateral involvement by lymphoma that is EBV-negative by EBER ISH. The specific mechanisms by which the adrenal microenvironment promotes lymphomagenesis are yet to be described.

Panel Diagnosis: IDD-LPD, HGCL, NOS

Intrathyroidal Diffuse Large B-Cell Lymphoma, anaplastic variant.

Dr. Matan D. Kadosh, Dr. Vrinda Shenoy, Dr. Wen Fan

Mount Sinai Morningside/West, Pathology, New York, USA

Case Description

A 67-year-old male with no significant past medical history presented with fatigue, unintentional weight loss, vocal fatigue, and an enlarging neck mass. No laboratory abnormalities. An ultrasound of the left thyroid lobe (7.4 x 3.8 x 5.7 cm) revealed a 5.4 cm nodule (TI-RADS 5).

Cytopathology reported heterogeneous lymphocytes with lymphohistiocytic aggregates and lymphoid tangles. A left thyroidectomy with central compartment node excisional biopsy was thus planned.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The sections show an effaced thyroid architecture with prominent atypical large multinucleated cells with some bizarre forms, and resembling Hodgkin Reed Sternberg (HRS)-like cells. The cells have prominent nucleoli, open chromatin, and pale-pink cytoplasm with some showing pyknosis and karyohexis. The background is predominately composed of large monomorphic cells resembling immunoblasts admixed with other histiocytes and mitotic figures arranged in a sinusoidal architecture.

Immunophenotype

The large, atypical cells stain positive for CD5, CD20, PAX5, Kappa(surface), OCT2, MUM1, Ki-67, C-Myc(rare), BOB1, CD79a, p53, EBER(rare), and Ki-67 (~90%). The large, atypical cell stain negative for CD3, CD10, CD15, CD21, CD23, BCL1, BCL6, SOX11, Lambda(surface), CD57, CD8, ICOS, LMO2, HGAL, IgD, CD30, ALK, PD1, CD4. The tumor microenvironment shows an increased CD4 to CD8 ratio of background T-cells with PD-1 like the CD4 staining pattern. p53 staining is mutant and overexpressed.

Cytogenetics

Interphase FISH results showed: •85% of cells POSITIVE for BCL6 (3q27) gene rearrangement and for IGH (14q32.3) gene rearrangement, together suggesting a possible t(3;14) translocation.

•77-79% of cells with 3 copies (gain) of MYC (8q24.21) and centromere 8, suggesting trisomy 8; and 84% with 3-5 copies (gain) of BCL2 (18q21).

•The cells were IGH::MYC [t(8;14)] and IGH::BCL2 [t(14;18)] fusion negative. MYC gene rearrangements were not detected.

Molecular Studies

N/A

Proposed Diagnosis

CD5+ Diffuse Large B-Cell Lymphoma (Activated B-cell Type), Anaplastic Variant, involving thyroid.

Interesting Feature(s)

•Primary thyroidal lymphoma is rare (<2% of extranodal lymphomas), PMID: 23714679.

•The bizarre and anaplastic large HRS-like cells are uncommon in DLBCLs, especially within the thyroid, PMID: 28319526.

•The increased ratio of CD4+ PD1+ to CD8+ PD1- T-cells suggest a tumor microenvironment impacted by immune surveillance dysregulation (and/or exhaustion) with treatment implications, especially with background mutant TP53 overexpression, PMID: 36561512 and 33787861.

•This case raises the question of proceeding with caution on cytopathology diagnosis and submit for flow cytometry

given the results of primarily lymphoid nodular tissue, as well as the need to further study anaplastic variants of thyroidal DLBCL.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-305

Intrathyroidal Follicular Lymphoma, CD23+; BCL2-

Dr. Matan D. Kadosh, Dr. Vrinda Shenoy, Dr. Wen Fan

Mount Sinai Morningside/West, Pathology, New York, USA

Case Description

30-year-old train engineer man with past medical history significant for Graves' disease (including family history) for 6 years; managed with methimazole and propranolol, asthma, and tobacco use. He had an exacerbation of Graves' Disease symptoms a year prior. Ultrasound showed a left thyroid lobe (7.5 cm) with a 2.1 nodular area that was slightly hypoechoic.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The intrathyroidal lymph node shows follicular architectural effacement and distortion of follicles by an atypical medium-sized lymphoid infiltrate with few normal background germinal centers.

Immunophenotype

The atypical small cells stained positive for CD20, PAX5, CD10, CD23, BCL6, OCT2, BOB1, LMO2, and Ki-67 (~50%). The atypical small cells were negative for CD3, CD5, BCL2, CD57, CD30, MUM1, MYC, BCL1, and STAT6. The tumor microenvironment showed a slight increased CD4+ to CD8+ T-cell ratio, along with a negative FOXP3. CD163 highlighted background histiocytes and occasional macrophages along with CD68.

Cytogenetics

Interpretation: Interphase FISH results showed 78% of cells POSITIVE for *IGH* (14q32.3) gene rearrangement, NOT involving *MYC* (8q24.21) or *BCL2* (18q21). *BCL6* (3q27) rearrangements were not detected.

Molecular Studies

Positive for clonal Immunoglobulin Light Chain (*IGK*) gene rearrangement (V and J/Kde regions).

A discrete band was identified, consistent with the presence of a monoclonal or oligoclonal B cell population.

Proposed Diagnosis

Follicular lymphoma, high grade (grade 3A), follicular pattern (CD23+; BCL2-)

Interesting Feature(s)

BCL2-, CD23+ Follicular lymphomas are uncommon tumors, with immunophenotypic, cytogenetic, and mutational presentations, PMID: 26481245.

The patient's tumor was negative for STAT6 immunohistochemistry suggesting a STAT6 mutation as well as CD23, which is seen in diffuse follicular lymphomas, PMID: 35851155.

The tumor has increased CD4+ to CD8+ ratio, indicating increased T-follicular helper and T-regulatory cells, which may suggest increased T-cell exhaustion, leading to immune evasion by the tumor cells and is possibly due to mutations in major histocompatibility class II, PMID: 33694181 and 35687817.

Tumor microenvironment associated macrophages play a possible role in the pathogenesis of follicular lymphoma by facilitating malignant favoring interactions with surrounding stromal cells and may confer a more favorable prognosis depending on treatment, PMID: 15548776, 38194685, and 27334853.

An increase in FOXP3+ regulatory T-cells would favor a better prognosis, however this tumor lacked FOXP3+ cells, PMID: 27334853.

Overall, this may be one of the few cases reported of Intrathyroidal follicular lymphoma in the setting of Graves' Disease.

Panel Diagnosis: FL CD23+, BCL2-

EA4HP26-LYWS-307

Peripheral T-cell Lymphoma Arising in Testis with CNS Involvement

Dr. Elizabeth Thai^{2,1}, Dr. Dean Fong^{1,2}, Dr. Ken Gatter², Dr. Todd Williams²

¹ VAMC Portland, Pathology and Laboratory Medicine Services, Portland, USA; ² Oregon Health & Science University, Department of Hematopathology, Portland, USA

Case Description

74-year-old male with remote liver and kidney transplants (1995) and splenectomy was evaluated for several months of intermittent, painless right testicular enlargement; progressive cognitive changes over a similar period were elicited on history. Ultrasound showed replacement of the right testis by a 5.3 × 3.5 × 4.2 cm heterogeneous mass, and a radical orchiectomy was performed. Grossly, the mass was white-tan, nodular, and firm with focal necrosis. Bone marrow biopsy showed a clonal plasma cell population without morphologic or immunophenotypic evidence of involvement; CSF studies and ENT evaluation were negative. FDG PET showed mildly increased metabolic activity in right temporal lobe. Six weeks later, he re-presented with worsening confusion and profound weakness; head CT showed a right temporal mass with midline shift, and an open biopsy showed CNS involvement. The patient was subsequently transitioned to hospice care and died shortly thereafter.

Biopsy Fixation Details

Testicle in RPMI; Testicle in FFPE; Brain in FFPE.

Frozen Tissue Available

None.

Details of Microscopic Findings

Testis:

H&E sections show diffuse involvement by an atypical lymphoid proliferation infiltrating atrophic seminiferous tubules. Tumor cells are large and pleomorphic, with vesicular chromatin and prominent nucleoli; necrosis, atypical mitotic figures, and occasional multinucleated forms are present. There is focal extension beyond the tunica albuginea and lymphovascular involvement; the epididymis is uninvolved. By immunohistochemistry (IHC), tumor cells are positive for CD3, CD7, CD4, CD8, CD56, CD43, BCL2, c-MYC, and GATA3, and negative for CD5, CD2, CD30, ALK-1, CD20, PAX5, CD10, Cyclin D1, TdT, and MUM1. Ki-67 highlights a high proliferative index (~80–90%). CD45 and BCL6 are equivocal. Granzyme B and perforin are positive; TIA-1 and EBER (ISH) are negative.

Brain:

H&E sections show large atypical lymphoid cells with an angiocentric distribution. By IHC, tumor cells are positive for CD3, CD7, BCL2, CD99 (dim, minor subset), granzyme B (subset), and perforin (minor subset), and lack significant expression of CD45, CD2, CD4, CD5, CD8, CD10, CD30, CD34, CD56, BCL6, PD-1, TdT, CD1a, TCR gamma/delta, MPO, ALK, OLIG2, GFAP, and EBER (ISH). Ki-67 highlights a high proliferative index (~70%). CD20 highlights rare, singly scattered, small B cells. CD138 and MUM1 highlight sparse polytypic plasma cells. HHV-8 is negative.

Immunophenotype

Flow cytometry performed on the testis identified an atypical T-cell population comprising ~70% of CD45+ events, with expression of dim CD2, partial sCD3, cCD3, dim CD7, CD8, dim CD45, partial CD56, partial CD79a; CD5, CD34, TdT, and CD1a were negative.

Cytogenetics

Not performed.

Molecular Studies

Comprehensive genomic profiling performed on the testis revealed a tumor mutational burden of 92 Muts/Mb and MSI-high microsatellite status. Pathogenic alterations were identified in *ASXL1*, *ATM*, *ATR*, *BCOR*, *BLM*, *CDKN2A*, *DDX3X*, *HRAS*, *IKZF3*, *JAK1*, *KMT2C (MLL3)*, *KMT2D (MLL2)*, *MAP3K6*, *MASH6*, *SETBP1*, *SOCS1*, *TET2*, *TP63*, and *TRAF2*. Clonal gene rearrangements were detected in TCR-gamma and TCR-beta.

Proposed Diagnosis

Testicular peripheral T-cell lymphoma (PTCL) in a post-transplant setting with CNS involvement.

Interesting Feature(s)

PTCL arising in testis is rare with few cases reported in the literature. This case demonstrates a PTCL arising in one immune-privileged site (testis) with dissemination to CNS in the post-transplant setting, with apparent restriction to immune-privileged compartments.

Panel Diagnosis: IDD-LPD, PTCL NOS

EA4HP26-LYWS-316

Leptomeningeal Marginal Zone Lymphoma with AL (kappa)-type Amyloidosis

Dr. Xiaojun Wu¹, Dr. Shih-Chun Lin², Dr. Khaled El-Shami³

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Case Description

A 71-year-old female with a history of Crohn disease treated with Skyrizi presented to the emergency department with severe headache and dizziness. Brain MRI revealed an avidly enhancing lentiform mass centered on the falx cerebri, measuring 5.8 × 1 × 4.2 cm, accompanied by leptomeningeal thickening and sulcal enhancement involving the left frontal and biparietal lobes. PET scan demonstrated a hyperdense, non-FDG-avid extra-axial left parafalcine mass without evidence of systemic lymphadenopathy, other neoplasms, or abnormal FDG uptake. The patient subsequently underwent a right frontal craniotomy with an interhemispheric approach for resection of the falcine lesion.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

The specimen shows dense fibrous tissue containing numerous granulomas composed of multinucleated giant cells surrounding amorphous eosinophilic material, some of which is perivascular. There is a prominent lymphocytic infiltrate with an overabundant population of plasma cells. Both lymphocytes and plasma cells are small, with mature

chromatin. Scattered large lymphocytes with features consistent with immunoblasts are present. No Hodgkin/Reed-Sternberg cells are identified, and no necrosis is observed.

Immunophenotype

The infiltrate was B-cell dominant (CD20⁺) with admixed CD3⁺ T cells and abundant CD138⁺ plasma cells. Most cells expressed CD79a, with a small subset positive for MUM1. Scattered CD30⁺ immunoblasts were present. Immunoglobulin staining showed a predominance of IgG⁺ cells, with rare IgM and IgD positivity and no significant IgA⁺ plasma cells. In situ hybridization demonstrated kappa light chain restriction. The IgG kappa lymphoplasmacytic cells lacked aberrant expression of CD5, CD10, CD56, CD117, cyclin D1, or CD30. Ki-67 proliferation index was 20–25%. EBV ISH and immunostain for syphilis were negative. Special stains (AFB, GMS) were negative. VVG highlighted perivascular amorphous deposits, and Congo red was positive. Mass spectrometry confirmed AL (kappa)-type amyloidosis.

Cytogenetics

N/A

Molecular Studies

IGH gene rearrangement was clonal.

Proposed Diagnosis

Leptomeningeal marginal zone lymphoma and AL-type amyloidosis

Interesting Feature(s)

First, the presence of a low-grade B-cell lymphoma confined to the leptomeninges is highly unusual. While leptomeningeal involvement can occur as a secondary manifestation of systemic lymphomas such as lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (Bing-Neel Syndrome), this patient showed no systemic disease or parenchymal CNS involvement, supporting a diagnosis of primary leptomeningeal marginal zone lymphoma.

Second, the coexistence of extensive amyloid deposition within the leptomeninges is exceptional. Amyloid in the CNS is typically linked to hereditary transthyretin amyloidosis, whereas AL-type amyloidosis usually affects visceral organs such as lung and heart. In this case, mass spectrometry confirmed AL (kappa)-type amyloid, likely produced by the lymphoplasmacytic component of the lymphoma. The deposits elicited a striking multinucleated giant cell reaction, adding complexity to the histopathology.

Finally, management posed challenges due to the blood-brain barrier limiting systemic therapy. The patient underwent surgical resection followed by adjuvant radiation, a pragmatic approach for localized, low-grade CNS lymphoma. This combination of primary leptomeningeal marginal zone lymphoma and localized AL amyloidosis represents a rare entity with diagnostic and therapeutic implications.

Panel Diagnosis: extranodal MZL

EA4HP26-LYWS-346

Dural Marginal Zone Lymphoma

Dr. Mohamed Rabie, Dr. Ruhi Hadwani, Dr. Amy Ku, Dr. Bachir Alobeid, Dr. Craig Soderquist

Columbia University Irving Medical Center, Pathology and Cell Biology, New York, Germany

Case Description

A 50-year-old woman with a history of multifocal motor neuropathy presented with new right-sided headaches. Brain MRI showed a right frontal extra-axial mass with subdural extension and edema. PET scan showed no systemic lymphadenopathy or bone lesions. The patient underwent a right frontal burr-hole biopsy.

Biopsy Fixation Details

The tissue is fixed in formalin.

Frozen Tissue Available

Not performed.

Details of Microscopic Findings

Histologic sections show fragments of fibrous tissue containing a diffuse to vaguely nodular proliferation of small to medium sized atypical lymphoid cells with irregular nuclei, coarse chromatin, indistinct nucleoli, and variable amounts of pale cytoplasm. There are no sheets of large cells.

Immunophenotype

By immunohistochemistry, the neoplastic cells are: CD20+, CD79a+, CD5-, CD10-, BCL6-, and BCL2+. CD10 and BCL6 highlight disrupted germinal centers, which are BCL2 negative. CD21 highlights expanded and disrupted follicular dendritic cell meshworks. The Ki-67 proliferation index is overall low in the neoplastic cells (~5%). Flow cytometry: CD19+, CD20+, CD79a+, CD10-, CD5-, CD22+, CD23-/+, CD200-/+, CD38+, CD43-, CD11c-, CD25-, CD103-, PD1-, IgM+/-, IgD-/+, CD123-/+, Kappa+, Lambda-.

Cytogenetics

Not performed.

Molecular Studies

A 702-gene targeted hematopoietic NGS panel shows a pathogenic NOTCH1 (c.7541_7542del; p.Pro2514Argfs*4) mutation. Additional variants of uncertain significance are identified in AMER1, ATM, CIITA, FBXO11, JAK1, JAK3, KLHL6, MAP3K1, and STAG2. Immunoglobulin Heavy Chain (IgH) Gene Rearrangement studies by Fluorescent PCR are positive.

Proposed Diagnosis

Dural marginal zone lymphoma.

Interesting Feature(s)

Dural marginal zone lymphoma (DMZL) is a rare indolent B-cell neoplasm, with just over 100 cases reported in the literature, and is considered an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue arising at a non-mucosal site. Prior studies have shown that DMZL shares genetic features with other marginal zone lymphoma (MZL) subtypes while exhibiting a distinctive genotype-phenotype correlation: cases with prominent plasmacytic differentiation are enriched for TNFAIP3 (A20) inactivation, whereas cases with monocytoid morphology (as described in our case) more frequently harbor activating NOTCH2 mutations, often with co-occurring TBL1XR1 alterations. Classic MALT-type translocations (e.g., IGH/MALT1) are typically absent. The present case is notable for harboring a pathogenic NOTCH1 mutation rather than the more characteristic NOTCH2 alterations reported in DMZL. Notably, this case also harbors a KLHL6 p.E547K variant, which has been reported as an uncommon but recurrent mutation in B-cell lymphomas.

From a therapeutic standpoint, activating NOTCH1 mutations in general may be clinically relevant, with potential sensitivity to NOTCH1 inhibitors and gamma-secretase inhibitors. Furthermore, data from non-Hodgkin lymphomas specifically suggest that NOTCH1 activation may be associated with responsiveness to PI3K inhibition.

This case highlights the emerging relevance of genomic profiling in dural marginal zone lymphoma, demonstrating a NOTCH1 alteration in an otherwise indolent, localized disease. Although the therapeutic implications remain incompletely defined, NOTCH1 pathway alterations may represent potential targets and underscore the need for further study to clarify their prognostic and therapeutic significance in this rare entity.

Panel Diagnosis: extranodal MZL

Primary ovarian diffuse large B-cell lymphoma with CDKN2A mutation

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¹ Central Institute, Valais hospital, Department of Pathology, Sion, Switzerland; ² Central Institute, Valais hospital, Department of Hematology and Hematology Laboratory, Sion, Switzerland

Case Description

A 79 year-old woman was referred to our hospital in December 2025 by her social worker due to asthenia, dizziness and involuntary weight loss (20kg). Medical history included hysterectomy for leiomyomas and hypercholesterolemia. Examination revealed bilateral lower extremity edema and fever (38.2 °C). Laboratory tests showed bicytopenia (haemoglobin 109 g/L, platelets 80 G/L), elevated C-reactive protein (53 mg/L) and marked hyperferritinemia (3913 µg/L). Thoraco-abdominal CT and pelvic MRI identified a left adnexal mass measuring 14 x 13 x 11 cm with areas of necrosis, causing compression of the left ureter and secondary pyelo-ureteral dilatation. A left common iliac adenopathy was present ; no other lymphadenopathy was detected. Given the strong suspicion of ovarian neoplasia, the patient underwent bilateral adnexectomy with a large epiploic biopsy.

Biopsy Fixation Details

Neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

The tumor consisted of a diffuse lymphoid proliferation composed of large atypical cells with centroblastic morphology and few, scattered small lymphocytes. Numerous mitotic figures and areas of extensive necrosis were present. The lymphoma cells infiltrated the fallopian tube. There was no residual ovarian parenchyma found on extensive sampling, and no evidence of an underlying low grade lymphoma. Epiploic tissue showed only focal infiltration by the lymphoma. The right ovary was unremarkable.

Immunophenotype

The tumoral cells strongly expressed B-cell markers (CD20, PAX5) and exhibited an activated B-cell phenotype (CD10-, BCL6+, MUM1+). They expressed BCL2, MYC (approximately 70% of cells, variable intensity) and were only focally positive for PD-L1 (SP263). CD30 was negative, and p53 showed a wild type staining pattern. No dendritic networks (CD21, CD23) or residual follicle mantles (IgD) were identified. The lymphoma cells showed strong IgM expression, without demonstrable light chain restriction. Proliferation index was high (>90%). EBER in situ hybridization was negative.

Cytogenetics

None

Molecular Studies

FISH analysis (Abbott, Break-Apart probes) showed no *BCL6*, *BCL2* or *MYC* rearrangement.

Targeted sequencing (NextSeq, Illumina) identified a *CDKN2A* R80* mutation with a variant allele frequency of 88%, classified as likely oncogenic according to OncoKB. No *MYD88* or *TP53* alterations were detected. NGS with a custom lymphoma panel has not yet been performed, as the case was recently diagnosed.

Proposed Diagnosis

Diffuse large B-cell lymphoma (DLBCL) arising in the ovary

Interesting Feature(s)

This case illustrates an unexpected diagnosis of diffuse large B-cell lymphoma, initially suspected clinically to be ovarian carcinoma. As staging showed no disease dissemination apart from a single locoregional lymph node, a primary ovarian origin was retained. The immunophenotype of this lymphoma is similar to primary large B-cell lymphomas of immune-privileged sites, in which *CDKN2A* deletions are reported, particularly in primary CNS and testicular DLBCL. In our case, targeted sequencing identified a truncating *CDKN2A* R80* mutation with a variant

allele frequency of 88%, consistent with likely biallelic inactivation or a mutation combined with deletion of the second allele. To our knowledge, *CDKN2A* alterations have not been specifically reported in primary ovarian diffuse large B-cell lymphoma, and therefore, this case contributes to the emerging genetic landscape of these rare tumors.

Panel Diagnosis: DLBCL, NOS

EA4HP26-LYWS-350

Testicular pleomorphic mantle cell lymphoma versus DLBCL with *CCND1* rearrangement

Dr. Alexander Anderson¹, Dr. Arinze Nkechi¹, Dr. Natasha Savage¹, Dr. Locke Bryan², **Dr. Mei Zheng**¹

¹ Medical College of Georgia/Augusta University, Pathology, Augusta, USA; ² Medical College of Georgia/Augusta University, HematoOncology, Augusta, USA

Case Description

A 49-year-old man presented with right testicular pain, swelling, and scrotal heaviness. Two years earlier, a small painful right testicular mass had been treated empirically as infection, after which he was lost to follow-up. He later developed rapid mass enlargement with worsening pain. Scrotal ultrasound showed findings concerning for torsion with hypoechoic areas suggestive of ischemia or infarction, a right radical orchiectomy was performed. Postoperative PET-CT demonstrated suspected involvement of the testicular vein with possible extension toward the inferior vena cava and right kidney causing right ureteral compression with hydroureteronephrosis. A diagnosis of B – cell lymphoma was rendered (see diagnosis). The patient was treated with the TRIANGLE regimen with intrathecal methotrexate prophylaxis (X4), followed by consolidative radiation to the contralateral testis and maintenance rituximab/zanubrutinib, and remains in remission, with the most recent surveillance CT chest/abdomen/pelvis in 12/2025.

Biopsy Fixation Details

Fixation: The specimen was received and fixed in 10% formalin.

Frozen Tissue Available

-

Details of Microscopic Findings

Histological examination revealed diffuse effacement of testicular architecture by a lymphoid neoplasm. The tumor was composed of pleomorphic lymphoid cells with irregular nuclear contours, vesicular chromatin, conspicuous nucleoli, and moderate amounts of cytoplasm. Marked nuclear pleomorphism and increased mitotic activity were present, with frequent apoptotic bodies.

Immunophenotype

Immunohistochemical studies demonstrated that the lymphoma cells are positive for B-cell markers, cyclin D1, BCL2, MUM1, and partial BCL6, negative for CD5, CD10, CD23 and SOX11. Ki67 shows high proliferative index of 75%; P53 stains 40% of the lymphoma cells. Peripheral blood flow cytometry identified a tiny population of B cells expressing CD19, CD20, partial dim CD10 and CD23, lacking CD5, with kappa light chain restriction, compatible with leukemic counter part of the lymphoma.

Cytogenetics

NHL FISH analyses revealed:

- T(11;14)(q13;q32) involving *CCND1/IGH* in 74% of analyzed cells
- Gain of BCL2 with trisomy and tetrasomy in 38% of analyzed cells

Molecular Studies

Pending B-cell lymphoproliferative disorder NGS Panel

Proposed Diagnosis

Testicular pleomorphic mantle cell lymphoma (MCL) with leukemic presentation

Interesting Feature(s)

Pleomorphic MCL and rare cyclin D1-positive DLBCL may show overlapping morphology, immunophenotype, and even CCND1 rearrangement, creating a significant diagnostic pitfall.

- In MCL, including pleomorphic/blastoid mantle cell lymphoma, the IG::CCND1 rearrangement arises from aberrant V(D)J recombination and is readily detected by dual color/fusion t(11;14) FISH.
- In contrast, cyclin D1–positive DLBCL was historically considered a post–germinal center lymphoma lacking CCND1 locus alteration (Jaffe, 2011).
- More recent studies have shown that CCND1 rearrangements may occur as secondary events in DLBCL, rather than the driver mutation in MCL, typically mediated by aberrant CSR/SHM, often involving non-IGH partners and frequently escaping detection by standard t(11;14) FISH probes (Özoğul, Campo, and Jaffe et al., 2024).
 - Additionally, non-nodal MCL commonly lacks SOX11 and CD5, further blurring the distinction from DLBCL.
- Overall, the findings favor pleomorphic MCL in our opinion.

Panel Diagnosis: MCL, pleomorphic

EA4HP26-LYWS-362

EBV+ DLBCL of the Ovary

Dr. Matan D. Kadosh, Dr. Vrinda Shenoy, Dr. Wen Fan

Mount Sinai Morningside/West, Pathology, New York, USA

Case Description

55-year-old woman with a history of HIV, kidney transplant (6 years ago for end stage renal disease), and flu-like illness a month prior to imaging. The patient was found (on PET/CT) to have an FDG avid right ovarian mass after scheduled abdominal CT scan for follow up on renal transplant. The PET scan found an ovarian mass suspicious for a primary malignancy vs PTLT. All laboratory values were within normal reference ranges. The FDG avid right ovarian mass lesion measured 3.5 x 3.1 cm (image 221), SUV max 26.3., suspicious for malignancy such as primary ovarian malignancy or less likely PTLT. Further, FDG avid portacaval adenopathy, suspicious for nodal disease and mildly FDG avid right lower quadrant mesenteric node, possibly metastatic or reactive was seen.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The biopsy specimen shows atypical medium to large lymphoid cells in the background of fibrous tissue.

Immunophenotype

The atypical lymphoid cells stain positively for CD20, C10, PAX5, MYC, BCL2, BCL6, CD45, PAX8, Ki-67 (~99%), MUM1, and OCT2, however the cells are negative for BCL1, CD5, CD3, CD23, CD30, LEF1, EBER-ISH, AE1/3, and CAM5.2.

Cytogenetics

Interpretation: Interphase FISH results showed 90% of cells with 3~6 copies (gain) of BCL2 (18q21), and 76% of cells with 3 copies (gain) of BCL6 (3q27). Cells were IGH::MYC [t(8;14)] and IGH::BCL2 [t(14;18)] fusion negative. BCL6 (3q27) and MYC (8q24.21) gene rearrangements were NOT detected.

Molecular Studies

Negative for clonal Immunoglobulin Light Chain (*IGK*) gene rearrangement (V and J/Kde regions).

No discrete clonal rearrangements were detected for TCR Beta and Gamma gene rearrangements, consistent with a polyclonal T-cell population.

Proposed Diagnosis

Large/High grade B cell lymphoma, arising in immune deficiency/dysregulation (EBV-, post-transplant and HIV settings)

Interesting Feature(s)

Gyn tract lymphomas comprise roughly 1.5% of all extranodal lymphomas, with ovarian primary Diffuse large B-cells being the most common, PMID: 35416104.

The setting of this HIV+ patient's lymphoma is surprising given there were no obvious symptoms and was found only incidentally during follow up scans for a renal transplant.

If believed that that this EBV- DLBCL is a part of Post-Transplant Lymphoproliferative Disorder, then this would be the second documented case in the literature, PMID: 20565880.

In one study, patients in the BCL2 extra copy group were associated with poor overall survival (OS) and progression-free survival (PFS) in a subset of 147 R-CHOP-treated patients. The presence of BCL2 copy number gains contribute to elevated BCL2 protein expression and serve as a predictor of treatment outcomes in DLBCL, PMID: 36167334.

Additionally, in one study, copy number gain of BCL6 was significantly associated with adverse outcome in DLBCL and linked with the ABC-like subtype, PMID: 24887457.

The patient's tumor is CD30- and EBV-, which is uncommon for this tumor presentation, PMID: 11112038 and 26780579.

Panel Diagnosis: IDD-LPD, DLBCL, NOS

EA4HP26-LYWS-364

Intravascular Large B-cell lymphoma

Dr. Ruhi Hadwani, Dr. Mohamed Rabie, PhD/MD Amy Ku, Dr. Bachir Alobeid, Dr. Mahesh Mansukhani, Dr. Craig Soderquist

NYP-Columbia University Irving Medical Center, Department of Pathology and Cell Biology, New york, USA

Case Description

A 70-year-old female with a history of sickle cell trait, hypertension, and hyperlipidemia was admitted for evaluation of altered mental status. MRI brain with/without contrast demonstrated multiple infarctions of possible embolic etiology. MRI T-spine finding with distal cord/conus and nerve root enhancement was concerning for CNS lymphoma versus sarcoid. CT Abdomen was also performed, and showed no other pertinent lesions. Brain biopsy was planned and performed for diagnosis and treatment. Dermatology was consulted for skin biopsy to rule out cutaneous involvement. A punch biopsy from the trunk was consistent with involvement by the patient's IVLBCL.

Biopsy Fixation Details

Formalin fixed

Frozen Tissue Available

Not performed

Details of Microscopic Findings

Histologic sections of the brain biopsy show reactive brain parenchyma with numerous small- to medium-caliber vessels distended by large atypical lymphoid cells. These cells exhibit round to irregular nuclear contours, variably

prominent nucleoli, and moderate amounts of cytoplasm, with rare mitotic figures. The atypical lymphoid cells are not observed in the brain parenchyma.

Immunophenotype

Immunohistochemical stains show the following phenotype: CD20+, CD79a+, CD5+, CD3-, MUM1 (strong)+, BCL6 (weak)+/-, CD10-, BCL2+/-, C-MYC+, CyclinD1-, CD30-, ALK1-, PDL1-/-, p53-, HHV8-. EBER in situ hybridization was negative. The Ki-67 proliferation index is very high in the neoplastic cells.

Cytogenetics

Not performed

Molecular Studies

Next generation sequencing studies of the micro dissected IVLBCL cells are pending and will be communicated to the committee when finalized.

Proposed Diagnosis

Intravascular Large B-cell Lymphoma

Interesting Feature(s)

Although historically classified as a distinct entity defined by selective intravascular growth, IVLBCL shows substantial molecular overlap with large B-cell lymphomas arising in immune-privileged sites. IVLBCL is frequently of non-GCB/ABC phenotype and is enriched for recurrent MYD88 (L265P) and CD79B mutations, aligning with the MCD genetic subtype described in DLBCL classification frameworks. IVLBCL also commonly exhibits immune-evasion features, including alterations involving the PD-L1/PD-L2 (9p24.1) locus and, in a subset, loss/downregulation of MHC class I/II antigen presentation. Across immune-privileged-site LBCL, immune escape is also prominent, often involving antigen-presentation pathway lesions (including HLA class I and B2M). Furthermore, confinement to the intravascular compartment has been proposed to represent a functionally immune-privileged microenvironment, analogous to established sanctuary sites such as the central nervous system and testis. Collectively, these shared genetic and immune-evasion features support viewing IVLBCL as biologically aligned with large B-cell lymphomas of immune-privileged sites, favoring classification frameworks that emphasize common molecular programs over anatomic distribution alone.

Panel Diagnosis: intravascular large B-cell lymphoma

EA4HP26-LYWS-369

Primary Breast Follicular Lymphoma with BCL2 Expression and Without BCL2 or BCL6 Rearrangement

Dr. Ece Ozogul, Prof. Arzu Ayhan, Prof. Ayşegül Uner

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Case Description

A 57-year-old woman presented with a gradually enlarging mass in the left breast over a six-month period. Radiologic evaluation classified the lesion as BI-RADS 4. An incisional biopsy was performed and initially reported as suspicious for low-grade lymphoma. The patient had no B symptoms at presentation. Axillary lymph nodes were radiologically benign, and positron emission tomography (PET) revealed no evidence of disease elsewhere. Subsequently, a lumpectomy was performed.

Biopsy Fixation Details

The lumpectomy specimen was fixed in 10% neutral buffered formalin and processed routinely for histopathologic and immunohistochemical examination.

Frozen Tissue Available

No frozen tissue was available.

Details of Microscopic Findings

Histologic examination revealed breast paranchyma infiltrated by a lymphoid neoplasm with a predominantly nodular/follicular growth pattern. In some nodules, follicular structures with germinal centers surrounded by thin mantle zones were also observed. The neoplastic follicles showed loss of polarization and were composed of small lymphoid cells with relatively monotonous smooth round nuclear contours, and admixed centroblasts.

Immunophenotype

Immunohistochemical studies demonstrated tumor cells positive for CD20, CD10, BCL6, and BCL2. CD23 showed patchy positivity. The neoplastic cells were negative for CD5 and Cyclin D1. The Ki-67 proliferation index showed intrafollicular variability, ranging from approximately 10% to 40%. The overall findings supported a diagnosis of follicular lymphoma.

Cytogenetics

Fluorescence in situ hybridization (FISH) analysis showed no rearrangements involving *BCL2* or *BCL6* genes.

Molecular Studies

No additional molecular studies were performed.

Proposed Diagnosis

Primary follicular lymphoma of the breast

Interesting Feature(s)

Primary follicular lymphoma of the breast is a rare extranodal entity that may radiologically mimic primary breast carcinoma. This case is notable for patchy CD23 expression in the absence of *BCL2* and *BCL6* rearrangements. Taken together, the extranodal localization, BCL2 protein expression without corresponding gene rearrangements, and CD23 positivity suggest that this case may belong to the spectrum of extranodal follicular lymphomas lacking *BCL2* rearrangement

Panel Diagnosis: follicular lymphoma

EA4HP26-LYWS-371

An Atypical Uterine Lymphoproliferation in a Transsexual Patient

Dr. Katrin S. Kurz¹, Dr. Alexander Fuchs², Prof. Georg Sauer², Prof. German Ott¹

¹ Robert Bosch Krankenhaus, Department of Clinical Pathology, Stuttgart, Germany; ² Robert Bosch Krankenhaus, Department of Obstetrics and Gynecology, Stuttgart, Germany

Case Description

A 36 year-old male transsexual patient (woman to man) and known HIV infection (viral load below detection limit) presented in 4/23 with abnormal bleeding starting in 9/22 in the absence of a menstrual cycle. He received hormonal therapy with Nebido since 2004. Mastectomy was performed in 2006 and ovariectomy in 2019. Other diagnoses are depression and struma with hypothyreosis. Further medications: Citalopram, L-Thyrox, Biktarvy. Lab findings were unremarkable (Hb 158g/l, Leuko 6,2 GIGA/l). A curettage was performed, followed by hysterectomy in 6/23.

Biopsy Fixation Details

Tissue from curettage and the uterus were fixed in 4% neutral buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

In both, the curettage and the hysterectomy specimen, a dense lymphocytic infiltration was seen in an irregular proliferating, occasionally hyperplastic endometrium, next to diffuse or vaguely defined nodular infiltrations consisting of cells with small- to medium- and sometimes large-sized vesicular nuclei with prominent nucleoli.

Immunophenotype

The infiltrate demonstrated dominant expression of CD20 and positivity for BCL6, whereas CD10 and BCL2 were negative. CD3 and CD5 revealed some interspersed T-cells. MUM1 was positive in some blasts and especially in numerous plasma cells in the background without clear light chain restriction. CD30 was negative. LMP and EBNA marked single cells each. Ki67 index was high (90%).

Cytogenetics

Epstein-Barr virus (EBV) encoded RNA in situ hybridisation (EBER ISH) disclosed some positive cells.

Molecular Studies

Clonal B-cell receptor rearrangement, detected in framework regions 3A (123 base pairs (bp)) and 2A (257bp) (Biomed).

Proposed Diagnosis

Florid reactive lymphoid hyperplasia/lymphoma-like lesion (LLL) of the female genital tract

Interesting Feature(s)

The unusual bleeding in reproductive age in a transsexual man under testosterone therapy and after ovariectomy revealed this rare LLL, usually occurring in the cervix and uncommonly in the endometrium, like in this case, mimicking diffuse large B-cell lymphoma. Blasts infiltrated diffusely the endometrium in the curettage, accompanied by lymphocytes, numerous granulocytes and polytypic plasma cells. Clonal rearrangement of the immunoglobulin heavy chain gene suggested clonal B-cell expansion. However, in the following hysterectomy specimen, a definite tumorous growth or myometrial infiltration could not be seen. Ultrasound revealed normal liver and spleen and enlarged lymph nodes were not described. In addition, on the background of known HIV infection, EBV-infected cells could be found immunohistochemically and by ISH. In summary these findings speak against malignant lymphoma and for florid reactive lymphoid hyperplasia or LLL of the female genital tract, respectively, despite of detected clonality (1,2).

1 Florid reactive lymphoid hyperplasia of the lower female genital tract (lymphoma-like lesion): a benign condition that frequently harbors clonal immunoglobulin heavy chain gene rearrangements. Geyer, J.T. et al., Am J Surg Pathol 2010, Feb;34(2):161-8.

2 The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Alaggio R. et al., Leukemia 2022, 36:1720–1748.

Panel Diagnosis: follicular hyperplasia in an immunocompromised patient

EA4HP26-LYWS-375

Diffuse Large B-Cell Lymphoma of the Ovary: Immune-Evasion Biology Beyond CNS and Testis

Dr. Barina Agil, Dr. Hugo Carillo Ng, Dr. Lucy Fu

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Case Description

A 38-year-old female presented with one month history of increasing abdominal bloating/distension, nausea, vomiting, along with shortness of breath and 30lb weight loss. Initial laboratory studies were remarkable for anemia, thrombocytosis, elevated LDH (729 units/L). Among the tumor markers, CA125 was markedly increased (2071.6 units/ml) while CEA and CA19.9 were within the reference ranges. CT scan revealed extensive peritoneal/omental nodularity, left adnexal mass (3.4 cm), ill-defined soft tissue thickening along the level of the sigmoid colon, mild ascites and bilateral pleural effusion.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Core biopsy of the left adnexal mass was performed (10% neutral buffered formalin) and peritoneal fluid was tapped. Both the specimens showed medium to large atypical lymphoid cells that had irregular nuclear contour, vesicular chromatin, conspicuous nucleoli, and moderate amount of cytoplasm.

Immunophenotype

Based on immunohistochemistry, the large atypical cells were positive for CD45, CD20, Pax-5, BCL6, MUM1, BCL2 (~100%), c-MYC (~80%), and negative for CD10, CD5 and EBER-ISH. Ki-67 demonstrated high proliferative index (~100%).

Cytogenetics

FISH analysis was negative for rearrangement of *MYC* and the *IGH::MYC* fusion.

Molecular Studies

Next generation sequencing identified mutations of *CCND3* p.(P284T) (23%), *EP300* p.(Q1036*) (14%) and *RHOA* p.(R5W) (4%).

Proposed Diagnosis

Pleural and cerebrospinal fluids cytology were negative for involvement. PET/CT showed no cervical or mediastinal lymphadenopathy.

Based on the overall findings, the diagnosis was consistent with primary ovarian diffuse large B-cell lymphoma (DLBCL), non-germinal B-cell-phenotype.

She was treated on DA-R-EPOCH, but developed sepsis and succumbed to her disease.

Interesting Feature(s)

This case highlights how primary ovarian DLBCL, although rare, behaves more like an immune-privileged site lymphoma (IP-L) than a typical nodal DLBCL. The CA125 elevation, peritoneal carcinomatosis-like spread, and adnexal mass underscores how ovarian DLBCL can clinically mimic epithelial ovarian cancer, delaying recognition. Immunophenotypically, the tumor showed a non-germinal center/activated B-cell phenotype, with strong BCL2 and c-MYC protein expression but no *MYC* rearrangement; an aggressive profile consistent with poor outcomes in extranodal DLBCL. The NGS findings (*CCND3*, *EP300*, *RHOA* mutations) are notable because they overlap with molecular alterations seen in IP-L (e.g., CNS and testicular), supporting emerging literature suggesting that primary LBCL of the ovary, breast, and skin may form a broader biologic group defined by immune-evasion mechanisms rather than anatomic location alone. Although this tumor lacked the *MYD88*^{L265P} mutation characteristic of the C5/MCD/MYD88 genetic subtype, its extranodal site, ABC phenotype, and IP behavior align conceptually with that category. The absence of cervical or mediastinal lymphadenopathy and negative pleural/CSF cytology further reinforce its primary extranodal origin, a pattern typical of IP-L. Clinically, the patient's rapid decline despite DA-R-EPOCH reflects the aggressive natural history of ovarian DLBCL and the broader challenge of treating lymphomas arising in immune-restricted environments, where impaired antigen presentation and unique stromal interactions may contribute to therapeutic resistance. Overall, this case adds to growing evidence that ovarian LBCL may belong to an evolving family of IP-LBCLs, with distinct biology, diagnostic pitfalls, and clinical behavior.

Panel Diagnosis: DLBCL, NOS

Primary Dural Follicular Lymphoma

Dr. María M. Roca¹, Dr. Hristo Iliev¹, Dr. Begoña Negro¹, Dr. Fina Climent²

¹ "Dr Josep Trueta" University Hospital, Pathology department, Girona, Spain; ² "Arnau de Vilanova" University Hospital, Pathology department, Lleida, Spain

Case Description

We present the case of a 69-year-old woman with a history of progressive diplopia over a two-year period, with no B symptoms. Brain MRI demonstrated an infiltrative lesion measuring 35 × 24 × 39 mm involving the meninges of the right infratemporal fossa and the skull base, with intracranial extension through both foramina ovale into the cavernous sinus. 18F-FDG PET/CT showed a moderately hypermetabolic infiltrative lesion in the aforementioned locations, without evidence of extracranial involvement. No FDG-avid lymphadenopathies were found in other areas. In view of the imaging findings, the patient underwent a right temporal craniotomy with excisional brain biopsy of the lesion.

Biopsy Fixation Details

Following fixation during 24 hours in 10% neutral buffered formalin, tissue underwent standard automated processing (graded alcohol dehydration, xylene clearing, and paraffin infiltration) and was embedded in paraffin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Histologic examination showed fragments of fibrous tissue with a dense lymphoid infiltrate displaying a mixed pattern—diffuse and vaguely nodular. Scattered nodules corresponding to secondary lymphoid follicles were identified and were composed of a mixture of centrocytes and centroblasts (the latter numbering fewer than 15 per high-power field). The follicles lacked polarization and showed no tingible body macrophages within germinal centers. Areas with diffuse growth pattern showed similar cytological features. No brain parenchyma involvement was detected. Bone marrow trephine biopsy was performed with no evidence of lymphoma infiltration.

Immunophenotype

The neoplastic cells expressed B-cell markers (CD20 and CD79a), as well as BCL2, BCL6, and CD10. CD3 and CD5 immunostains highlighted only a minimal population of accompanying T lymphocytes. Within germinal centers, a residual follicular dendritic cell meshwork with central loss was demonstrated by CD23 staining. The Ki-67 proliferative index was around 20%

Cytogenetics

Fluorescence in situ hybridization (FISH-BA) demonstrated a presence of *BCL2* gene translocation. However, no *BCL6* gene rearrangement was detected.

Molecular Studies

Next-generation sequencing identified several pathogenic or likely pathogenic variants in *TNFRSF14* (VAF 40.4%), *CREBBP* (VAF 38.9%), *CARD11* (VAF 18.8%), and *EZH2* (VAF 18.6%). Variants of uncertain significance (VUS) were also detected in *CCND1*, *MYC*, *BCL2*, and *PIM1*.

Proposed Diagnosis

Given the histologic, immunophenotypic, and molecular features, together with the extra-axial location of the mass, and the absence of systemic disease or prior history of lymphoproliferative disorder, the final diagnosis was Primary Dural Follicular Lymphoma.

Interesting Feature(s)

Primary dural follicular lymphoma is exceedingly rare. To date, only 9 cases of this entity have been reported, including our case. Following surgical biopsy, the patient received combined chemoimmunotherapy and local radiotherapy, achieving an excellent response and remaining disease-free 36 months after diagnosis.

EA4HP26-LYWS-397

Primary breast large B cell lymphoma with MYD88 mutation.

Dr. Seher Yuksel, Dr. Tugfan Kokturk, Prof. Isinsu Kuzu

University of Ankara School of Medicine, Pathology, Ankara, Germany

Case Description

A 42-year-old female with two hypoechoic areas in the left breast measuring 12 × 36 mm and 11 × 29 mm, without any lymph node involvement was biopsied and diagnosed as lymphoma in 2021. Postoperative PET/CT performed within 1 month demonstrated several involved lymph nodes located in the left axilla (SUV max: 10.0). No other sites of disease involvement were detected. After three cycles of treatment, follow-up PET/CT demonstrated complete regression of the previously described lesions. During follow-up in 2023, a mass was detected in the left breast, and core needle biopsy was interpreted as recurrent high-grade lymphoma. High dose treatment with bone marrow transplantation performed but she did not recover and lost in 2023.

Biopsy Fixation Details

Buffered formalin

Frozen Tissue Available

no

Details of Microscopic Findings

The lesion from breast tissue was well circumscribed composed of large pleomorphic lymphoid cells with increased mitosis

Immunophenotype

The described large atypical cells show diffuse strong expression of CD20, BCL-2, BCL6, CD10, and MUM1. The proliferation index with Ki-67 is very high, around 80%. MYC expression is was present 25-30% of the tumor cells. T cells in tumor microenvironment was very few.

Cytogenetics

BCL2, MYC, BCL6 and IGH rearrangement was not observed

Molecular Studies

GENE EXONMUTATIONVAF%READFUNCTIONTIER

MYD885 L252P 54 70 gain 1A

ACTB 4 R210C 13 164 loss 3

ACTB 6 E364K 8,33 84 loss 3

Proposed Diagnosis

Primary breast large B cell lymphoma with MYD88 mutation

Interesting Feature(s)

Primary DLBCL of breast is a very rare and aggressive disease. This case has a very fast development and even in a month period its spread demonstrated by PET CT. Characteristic T cell poor microenvironment was present. Phenotype is presenting memory like late germinal center B cells. The molecular profile with MYD88 mutation was one of the expected diagnostic characteristics and should be performed for guiding the treatment. The other mutations are not confirmed for explaining the more aggressive clinical course of the disease.

Panel Diagnosis: DLBCL, NOS

Primary Extranodal Marginal Zone B cell lymphoma of the Left Ovary with involvement of Left fallopian tube and Left Anterior Endomyometrium.

Dr. Mustafa Al-Kawaaz¹, PhD/MD student Catherine Spencer², Dr. Mackenzie M. Dent¹, Dr. Ju-Hsien Chao³, Sarah Todd⁴, Dr. Samer Z. AlQuran¹

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Case Description

Clinical History: A 78-year-old nulliparous woman with a several-year history of intermittent vulvar burning managed with topical estrogen presented with acute worsening vulvar pain. Transvaginal ultrasound revealed a left adnexal tubular mass measuring 9.2 × 3.2 × 4.5 cm, two small endometrial polyps, and a thickened endometrium. She reported mild lower back pain and intermittent bilateral lower pelvic tenderness without systemic symptoms. Pelvic examination and preoperative laboratory studies were unremarkable.

The patient underwent robotic total hysterectomy with bilateral salpingo-oophorectomy. Intraoperative frozen section of the left adnexal mass involving the left fallopian tube demonstrated a small blue cell tumor, favoring lymphoma, prompting surgical staging with infracolic omentectomy and left pelvic sentinel lymph node sampling. Gross examination revealed a left adnexal mass involving the ovary and fallopian tube measuring 8.0 × 4.5 × 3.0 cm. Postoperative CT scan of the chest and abdomen showed no significant lymphadenopathy, splenomegaly or evidence of residual disease. A PET scan showed no foci of abnormal FDG activity in the chest, abdomen or pelvis. A hepatitis panel and HIV testing were nonreactive and lactate dehydrogenase was within normal limits. SPEP showed no monoclonal protein; serum free kappa light chain 12.8; serum free lambda light chain 9.4; and kappa:lambda 1.36.

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

No

Details of Microscopic Findings

Examination of histologic sections of the left ovary revealed effacement of the architecture by a diffuse atypical lymphoid infiltrate composed predominately of small CD20(+) B-lymphocytes, including few with pale cytoplasm. Similar findings were noted in the left anterior endometrium, myometrium, serosa, and left fallopian tube. The right fallopian tube and ovary, cervix and posterior uterine wall were not involved by lymphoma. The left pelvic sentinel lymph node was not enlarged but showed atypical lymphoid infiltrate worrisome for involvement by low grade B-cell Lymphoma. No evidence of large cell lymphoma was seen. Sections from the omentum were negative.

Immunophenotype

Immunohistochemical studies showed that the neoplastic lymphoid cells were positive for PAX-5, and IgM, with low labeling of nuclei by Ki-67 (~10%). They were negative for CD5, Cyclin D1, LEF1, IgG and CD30. CD3 was positive in small T lymphocytes. ISH for EBV encoded RNA (EBER) was negative.

Flow cytometric immunophenotyping performed on fresh tissue from the left ovary demonstrated an abnormal population of kappa-restricted small B-cells that were CD20(+), CD19(+), CD79b(+), CD22(+), CD5(-), CD10(-), CD23(-) and CD38(-). The neoplastic cells comprised ~70% of lymphocytes. No abnormal plasma cells were identified.

Cytogenetics

Not performed.

Molecular Studies

MYD88 Mutation(s): Detected

Mutation(s) Detected c.794T>C (p.L265P)

CXCR4 Mutation Analysis: Not Detected

Proposed Diagnosis

Extranodal marginal zone B cell lymphoma (EMZL) of the ovary, fallopian tube, and uterus, and left pelvic sentinel lymph node.

Interesting Feature(s)

Primary lymphoma of the female genital tract is a very rare condition with the majority being DLBCL. The majority of EMZL in the female genital tract originate in the uterus with very few cases of the fallopian tube or ovary. We describe a very rare case of extranodal marginal zone B-cell lymphoma arising primarily in the left ovary and involving the left fallopian tube as well as anterior left uterus, and left pelvic sentinel lymph node, with MYD88 Mutation.

Panel Diagnosis: extranodal MZL

EA4HP26-LYWS-430

Primary Diffuse Large B cell Lymphoma arising as a primary ovarian neoplasm

Dr. Osvaldo Padilla, Dr. Eric Kawana, Dr. Roberto Gamez

Texas Tech University Health Science Center El Paso, El Paso, USA

Case Description

A 66 year old female presents with abdominal pain for which a CT scan revealed a 4 cm mass in the right ovary. A total hysterectomy and bilateral salpingo-oophorectomy showed a diffuse large B cell lymphoma (DLBCL) in association with a follicular lymphoma, grade 3A (FL G3A).

Biopsy Fixation Details

The tissue was process as follows:

1. **Fixation:** Place the core in fixative (buffered formalin).
2. **Processed by dehydration & clearing:** Pass through graded alcohols (ethanol) then xylol (or xylene).
3. **Paraffin Embedding:** Impregnate with molten paraffin wax and embed to form a solid block.
4. **Sectioning:** Cut thin sections (1-4 µm) from the block using a microtome.
5. **Staining:** H&E (Hematoxylin & Eosin) and Immunohistochemistry (IHC)

Frozen Tissue Available

None

Details of Microscopic Findings

The microscopic findings showed a nodular pattern with areas of diffuse sheets of cells. Closer magnification showed a combination of smaller and larger lymphocytes with some areas showing a predominantly smaller cells (corresponding to a follicular lymphoma Grade 3A) and areas with predominantly larger cells (corresponding to a DLBCL).

Immunophenotype

DLBCL is CD10+, CD20+, CD79a+, PAX5+, BCL2+, BCL6+, and Ki-67 being about 50% nuclear staining. Areas of follicular lymphoma grade 3A showed a similar IHC profile as the DLBCL, but with a Ki-67 being 10-20% staining.

Cytogenetics

None

Molecular Studies

FISH IGH (14q32.33) :BCL2 (18q21.33) probe : POSITIVE (89% of cells)

FISH MYC (8q24.21) probe: NEGATIVE

FISH BCL6 (3q27.3) probe: NEGATIVE

Proposed Diagnosis

Right ovary with a Diffuse Large B cell Lymphoma (germinal center subtype) associated with areas of follicular lymphoma (grade 3A).

Interesting Feature(s)

- Our case demonstrate follicular lymphoma (grade 3A) associated with diffuse large B cell lymphoma that appears to be an ovarian primary.
- Non-Hodgkin lymphomas (NHLs) uncommonly involve the gynecologic organs, since there is a lack of lymphatic tissue in these organs. However, when NHL does involve these gynecologic organs, the ovary is a more common anatomical site (1).
- Ovarian non-Hodgkin lymphomas (NHLs) are more frequently due to systemic NHL disease with secondary involvement of the ovary and/or fallopian tubes (1).
- Primary (or localized) ovarian NHL is even more rare, representing less than 10% of all ovarian NHLs, 0.5% of NHLs, and 1.5% of ovarian tumors (2).
- An ovarian primary is favored based on clinical localization; stage of IIE.
- Abdominal pain is the common symptom described in other similar cases as ours (3,4,5)

Panel Diagnosis: DLBCL, transformed from FL3A

EA4HP26-LYWS-436

Don't forget CD20 in breast implant-associated lymphoma

Dr. Catherine Chassagne-Clement¹, Dr. Julie Gervasoni², Dr. Emmanuel Beillard³, Dr. Yann Guillermin⁴

¹ Centre Léon Bérard, Biopathologie, Lyon, France; ² Centre Léon Bérard, Biopathologie, Lyon, France; ³ Centre Léon Bérard, Biopathologie, Lyon, France; ⁴ Centre Léon Bérard, Oncohématologie, Lyon, France

Case Description

A 51-year-old female with history of bilateral breast implants for cosmetic purposes (Allergan macrotextured implant in 2007). She presented in 2022 with a unilateral effusion around the left breast implant. Fine needle aspiration revealed large atypical lymphoid cells. A bilateral capsulectomy was performed. The left capsule was covered by a floating material without thickening or tumoral masse. Histological and immunohistochemical examination resulted in the diagnosis of EBV-associated large B-cells lymphoma. There was no B symptoms. The FDG PET imaging revealed no hypermetabolic lesion either.

Biopsy Fixation Details

4% neutral buffered formol

Frozen Tissue Available

No

Details of Microscopic Findings

The inner surface of the capsule was covered by fibrin and necrotic material. This material encompassed small aggregates of large lymphoma cells.

Immunophenotype

The lymphoma cells stained positively for CD30, CD20, CD79a, PAX5, MUM1. The cells were negative for CD2, CD3, CD5, CD7, BCL6, CD10 and MYC. The Ki67 proliferative index was high (80%). These cells were also positive for EBV by *in-situ* hybridization with a type III latency stage (LMP1+/EBNA2+).

Cytogenetics

A FISH analysis with break-apart probe for MYC revealed no rearrangement.

Molecular Studies

A NGS study using a customized panel of 150 genes revealed no pathogenic variant.

Proposed Diagnosis

Fibrin-associated large B-cell lymphoma (WHO 2022).

Interesting Feature(s)

This case illustrates a rare type of breast implant-related B-cell lymphoma. The EBV association with a type III latency stage suggested a local immune escape of the EBV+ B-cells. Hypoxic mechanisms might also be involved.

Panel Diagnosis: Fibrin-associated LBCL

EA4HP26-LYWS-445

Primary Adrenal Diffuse Large B Cell Lymphoma

Dr. Scott A. Ely

Memorial Sloan Kettering Cancer Center, Pathology/Hematopathology, New York, USA

Case Description

85yo M without significant PMH had CT of chest for chronic cough. The CT showed a new left adrenal mass. MRI showed 8.7 x 4.8 cm left adrenal mass. No other lesions were identified. A left adrenalectomy was performed.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

Available

Details of Microscopic Findings

Diffuse sheets of large transformed lymphocytes with scant cytoplasm, ovoid, vesicular nuclei with disbursed chromatin and multiple small nucleoli. No plasmacytoid differentiation. Focal necrosis.

Immunophenotype

AI Image Analysis			
Marker	% of all cells	Average Intensity	NB
CD20	87%	2+	
CD3	*23%	0	*non-neoplastic
CD5	*21%	0	*non-neoplastic
CD10	0%	na	
BCL6	16%	1+	
MUM1	39%	2+	
BCL2	97%	3+	

Ki67	88%	2+	
**CD23	0%	na	**FDC meshworks absent
CMYC Mean	30%	0	
CMYC High	78%	1+	
CMYC Low	22%	0	
Cyclin D1	0%	0	
EBER ISH	0%	0	

Cytogenetics

No evidence of BCL6 (3q27.3) rearrangement, however, gain (one to two extra copies) of BCL6 detected in 35% of cells. No evidence of BCL2 (18q21.3) rearrangement, however, gain (one to two extra copies) of BCL2 detected in 20% of cells. No evidence of MYC (8q24.2) rearrangement,.

Molecular Studies

POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS IN CLINICALLY VALIDATED PANEL:

1. MYD88 (NM_002468) exon5 p.L265P (c.794T>C)

POSITIVE FOR THE SOMATIC ALTERATIONS, INVESTIGATIONAL PANEL: RRAS,

CDKN2Ap16INK4A, ACTG1, ARID5B, B2M, BCR, BTG1, CBLB, CD58, EP300, ETV6 , FAT1, HDAC7, HLA-B, IRF4, KDR, KLHL6, KMT2D , MPEG1, PIM1, ZFH4

Proposed Diagnosis

9680/3 Diffuse large B-cell lymphoma, activated B-cell subtype-WHO5 and ICC

-However, the striking similarity to IP-LBCL merit consideration of inclusion of primary adrenal DBLCL in the IP-LBCL category in future classifications

Interesting Feature(s)

Among immune-privileged (IP) sites, the CNS, testis, and vitreoretina are recognized as being distinct from other sites in that the microenvironment gives rise to DLBCLs with unique clinical, immunophenotypic and genomic features. The similarities of this primary adrenal DBLCLs (PADLBCL) to other IP lymphomas support the idea that PADLBCL is distinct from non-IP site DLBCLs, and consideration should be given to formal inclusion of PADLBCL primary large B-cell lymphomas (LBCLs) of immune-privileged sites (IP-LBCLs).

PADLBCL is rare, with only ~100 in the literature. Whereas nodal DLBCL median overall survival (OS) is ~8 years, primary CNS DLBCL OS is 36 months, and testicular DBLCL OS is 16 months for stage III/IV disease. One study showed PADLBCL OS to be only 14 months. This suggests that R-CHOP and other standard therapies are not effective in PADLBCL. As such, primary adrenal localization should be emphasized.

The immune microenvironment has not yet been extensively studied in this case, but the relative paucity of background T cells is noted.

The activated, non-germinal center immunophenotype in this case is typical of IP lymphomas.

Studies suggest that the unique testicular microenvironment facilitates the growth of MYD88-mutated lymphomas and that the adrenal cortex shares such features. Whereas MYD88 mutations are found in as few as 17% of nodal DLBCL, they are found in 80% of primary CNS and testicular cases. In addition to MYD88, this case showed mutations of PIM1 and CDKN2A, which also are common in IP-LBCL. There were multiple mutations in B2M and other mutations consistent with loss or down-regulation of HLA antigen expression, an immune-escape feature that also is common in IP-LBCL.

In summary, the findings in this case are strikingly similar to other IP-LBCL and support formal inclusion of PADLBCL as an IP-LBCL.

Panel Diagnosis: DLBCL, NOS

Primary Breast DLBCL with Double Expressor Phenotype in a Patient with Hepatitis C History

Dr. Khadijah A. Moustafa¹, Dr. Cesar Gentile², Dr. Rodolfo Henrichlobo¹, Prof. Daisy Alapat¹

¹ UAMS, Pathology, LR, USA; ² UAMS, Hematology- Oncology, LR, USA

Case Description

A 66-year-old female with past medical history of hyperlipidemia, hypothyroidism, osteoarthritis, and hepatitis C presented with a self-palpated right breast mass.

Mammogram: Right Breast:- Two suspicious masses: a 3.1 cm round hyperdense mass with circumscribed margins at the 12:00 axis (15 cm from nipple), and a 1.6 cm mass at the 11:00 axis (15 cm from nipple). Both lesions were classified as BI-RADS Category 4. Ultrasound: Both masses demonstrated similar findings with a hypoechoic rim, hypoechoic center, and hypervascular. PET/CT revealed Stage IIE disease: 4.6 × 3.9 cm right breast mass (SUV 19), adjacent nodule 2 × 2 cm (SUV 13), and 0.7 cm right axillary lymphadenopathy (SUV 5.4) with no other sites of disease.

Procedure:- Vacuum-assisted ultrasound-guided core biopsy of both lesions and staging Bone marrow biopsy. The patient has achieved complete metabolic remission on glofitamab following failure of both R-CHOP and subsequent CRISPR-Edited Allogeneic Anti-CD19 CAR-T Cell Therapy in Patients with Relapsed/Refractory B Cell Non-Hodgkin Lymphoma (ANTLER). Currently patient remains on close observation with no plans for allogeneic hematopoietic cell transplantation at this time.

Biopsy Fixation Details

Fixed in 10% neutral buffered formalin and small fresh tissue allocated for flow cytometry and cytogenetics.

Frozen Tissue Available

No

Details of Microscopic Findings

Both specimens demonstrated a diffuse proliferation of atypical large lymphoid cells with centroblastic morphology infiltrating breast fibroadipose tissue.

Immunophenotype

- Positive: CD20, CD79b, CD22, c-Myc, BCL2, MUM1 and Ki-67 proliferation index:75%
- Negative: CD3, CD5, CD10, CD21, CD30, BCL1, BCL6
- EBER (EBV-encoded RNA): Negative
- Flow cytometry: CD20+/CD19+ B lymphocytes with surface kappa light chain restriction, high forward scatter, and expressing CD22, CD79b and negative for CD5, CD10, CD38, and CD30.

Cytogenetics

Conventional cytogenetics: 45,XX,-18 with low mitotic index

FISH studies: Negative for BCL6, MYC, and BCL2 rearrangements; negative for t(14;18)

Molecular Studies

Not Performed

Proposed Diagnosis

Diffuse large B-cell lymphoma (DLBCL), NOS, involving the right breast, with double expressor phenotype (BCL2+/MYC+) and non-germinal center B-cell (non-GCB) immunophenotype.

Interesting Feature(s)

This case demonstrates several interesting features: (1) Primary breast DLBCL presenting as a palpable mass in a 66-year-old female, representing a rare extranodal presentation accounting for 1% of all non-Hodgkin lymphomas; (2) Double expressor lymphoma (DEL) phenotype with co-expression of BCL2 (>50%) and c-Myc (>40%) by immunohistochemistry, which is associated with worse prognosis and occurs in approximately 30% of DLBCL cases; (3) Non-GCB phenotype (CD10-negative, MUM1-positive, BCL6-negative) with DEL features, a combination

that carries poor prognostic implications; (4) History of treated hepatitis C, which has been associated with increased risk of B-cell lymphomas.

The presentation in a patient undergoing CAR-T evaluation emphasizes the importance of further subclassification and comprehensive immunophenotypic assessment in guiding advanced therapeutic strategies.

Panel Diagnosis: DLBCL, NOS

LYMPHOMA SESSION IV | Nodal and extranodal T-cell lymphomas with prominent histiocytes, e.g. Lennert lymphoma, anaplastic large cell lymphoma (ALCL), associated with haemophagocytic lymphohistiocytosis (HLH); excluding cutaneous lymphoma

EA4HP26-LYWS-11	Splenic gamma-delta T cell lymphoma (non HSTCL) NOS with post splenectomy severe HLH
EA4HP26-LYWS-13	Anaplastic Large Cell Lymphoma with Leukemic Relapse Misdiagnosed as Primary Hemophagocytic Lymphohistiocytosis
EA4HP26-LYWS-14	A Case of Lymphoepithelioid Variant of Peripheral T-cell lymphoma, NOS, in a 16-year-old Female
EA4HP26-LYWS-15	From skin lesion to bone marrow: T-cell lymphoma-NOS with prominent lymphohistiocytic infiltrate.
EA4HP26-LYWS-19	Nodal T-follicular helper cell lymphoma, angioimmunoblastic type, with granulomata
EA4HP26-LYWS-23	Synchronous T-follicular helper cell lymphoma (TFHL), NOS with Lennert-like features and TFHL, angioimmunoblastic type with identical clonality
EA4HP26-LYWS-25	Lennert lymphoma with a genetic profile
EA4HP26-LYWS-33	Atypical Clonal CD4-positive T-cell Infiltrate in a Patient with an Isolated Sinus Cavity Mass
EA4HP26-LYWS-34	Hemophagocytic lymphohistiocytosis associated with a primary bone marrow peripheral T-cell lymphoma mimics EBV-negative aggressive NK cell leukemia
EA4HP26-LYWS-42	Nodal CD4+ T-cell lymphoma with Lennert-like morphology, incomplete TFH immunophenotype and molecular findings suggestive of nodal T follicular helper cell lymphoma (nTFHL)
EA4HP26-LYWS-55	ALK+ anaplastic large cell lymphoma (ALK+ ALCL), lymphohistiocytic variant: widespread nodal and extranodal dissemination with associated macrophage activation syndrome (MAS)
EA4HP26-LYWS-63	EBV-Positive Lymphoproliferative Disorder and Subsequent Follicular Helper T-Cell Lymphoma Share Identical Genetic Alterations
EA4HP26-LYWS-74	Lennert Lymphoma
EA4HP26-LYWS-78	Lennert-like nodal EBV+ T- and NK-cell lymphoma
EA4HP26-LYWS-79	Extranodal ALK Positive Anaplastic Large Cell Lymphoma with Rare Fusion Partner and Fulminant Course Complicated by Hemophagocytic Lymphohistiocytosis
EA4HP26-LYWS-80	CD4-Positive Lymphoepithelioid Lymphoma (CD4+ Lennert Lymphoma): An entity probably lying within the spectrum of nodal TFH lymphomas
EA4HP26-LYWS-83	Lennert's lymphoma (lymphoepithelioid variant of peripheral T-cell lymphoma, NOS) mimicking reactive (granulomatous) lymphadenopathy
EA4HP26-LYWS-98	Indolent CD4 positive clonal T-cell lymphoproliferative disorder, EBV negative occurring in post-transplant setting
EA4HP26-LYWS-114	TCR-Silent Nodal Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL, NOS) with Malignancy-Associated Fulminant Hemophagocytic Lymphohistiocytosis (HLH)
EA4HP26-LYWS-123	ALK-positive anaplastic large cell lymphoma in a patient status post CAR-T therapy for multiple myeloma

EA4HP26-LYWS-127	T-cell lymphoma with prominent histiocytes
EA4HP26-LYWS-132	Lennert lymphoma GATA3+
EA4HP26-LYWS-137	Follicular Helper Cell T-cell Lymphoma, Angioimmunoblastic Type, with Prominent Histiocytic Infiltrate Including Multinucleated Giant Cells
EA4HP26-LYWS-156	Peripheral T-Cell Lymphoma (NOS), lymphoepithelioid variant.
EA4HP26-LYWS-160	Rhyme or reason: CD8+ Histiocyte-rich T-cell lymphoma with AITL-like genetics and a hint of POEMS
EA4HP26-LYWS-161	T-cell lymphoma with prominent histiocytes and angioimmunoblastic features
EA4HP26-LYWS-164	A Case of Limited Stage T-Cell Lymphoma with T Follicular Helper Cell Phenotype
EA4HP26-LYWS-179	Systemic/ Leukemic Involvement by ALK+ Anaplastic Large Cell Lymphoma with Associated Hemophagocytic Lymphohistiocytosis
EA4HP26-LYWS-186	ALK-positive Anaplastic Large Cell Lymphoma, lymphohistiocytic pattern
EA4HP26-LYWS-190	Boundaries Between Reactive and Neoplastic: A Diagnostic Challenge in Nodal T-Follicular Helper Cell Lymphoma
EA4HP26-LYWS-193	Nodal T follicular helper cell lymphoma NOS with Lennert-like Granulomas Masquerading as Lennert Lymphoma: A Prototypic Pitfall in Epithelioid Histiocyte-Rich (Granulomatous) T-cell lymphoma
EA4HP26-LYWS-197	Unusual immunophenotypic and molecular features of nodal T-cell lymphoma with prominent histiocytes, designated as anaplastic large cell lymphoma as consensus diagnosis at multidisciplinary meeting
EA4HP26-LYWS-202	T-cell lymphoma with lymphoepithelioid (Lennert-like) morphology and TFH immunophenotype
EA4HP26-LYWS-216	Evolution of Cytotoxic Peripheral T-cell Lymphoma with Lennert Pattern
EA4HP26-LYWS-217	Nodal TFH-cell lymphoma NOS masked by epithelioid cells and apoptotic necrosis
EA4HP26-LYWS-225	T/NK-cell lymphoma with EBV related hemophagocytosis and with a bone marrow manifestation
EA4HP26-LYWS-253	<i>Lymphoepithelioid lymphoma (Lennert lymphoma) with unusual phenotype</i>
EA4HP26-LYWS-256	Primary Cutaneous T cell lymphoma with Granulomatous Features with Subsequent Nodal Lymphoepithelioid PTCL
EA4HP26-LYWS-269	Nodal T-cell follicular helper (TFH) lymphoma, angioimmunoblastic type (nTFHL-AI), with extensive granulomatous inflammation.
EA4HP26-LYWS-280	Nodal T follicular helper cell lymphoma, angioimmunoblastic type, with prominent lymphoepithelioid infiltrate
EA4HP26-LYWS-284	Peripheral T cell lymphoma (Lennert lymphoma) with an unusual phenotype and associated EBV viremia
EA4HP26-LYWS-295	Peripheral T-cell lymphoma, not otherwise specified, lymphoepithelioid variant (Lennert's lymphoma)
EA4HP26-LYWS-298	EBV(+) lymphoma with abundant Reed-Sternberg-like cells, favor T-cell lymphoma. Numerous hemophagocytic histiocytes, supporting a concomitant diagnosis of hemophagocytic lymphohistiocytosis (HLH).
EA4HP26-LYWS-311	Pancytopenia in a Patient with History of Chronic Lymphocytic Leukemia
EA4HP26-LYWS-312	Fulminant Case of ALK+ Anaplastic Large Cell Lymphoma
EA4HP26-LYWS-315	Pediatric T-cell Lymphoma (ALCL or SMARCB1 deficient?)

EA4HP26-LYWS-334	A rare and aggressive entity: CD30/CD56/CD8-positive primary bone marrow T-cell lymphoma associated with EBV infection and HLH
EA4HP26-LYWS-340	A syncytial CD30+ lymphoma
EA4HP26-LYWS-341	Nodal T follicular helper cell lymphoma, angioimmunoblastic type, with prominent clusters of epithelioid histiocytes.
EA4HP26-LYWS-345	NODAL T-FOLLICULAR HELPER CELL LYMPHOMA, ANGIOIMMUNOBLASTIC TYPE, WITH HODGKIN-LIKE CELLS
EA4HP26-LYWS-349	Peripheral T-Cell Lymphoma, NOS With Prominent Granulomatous Inflammation: A PTCL-TBX21 (TH1) Biologic Subtype Mimicking Sarcoidosis
EA4HP26-LYWS-358	ALK-negative anaplastic large cell lymphoma with atypical morphology (small cell variant)
EA4HP26-LYWS-360	ALK-negative anaplastic large cell lymphoma, <i>TP63</i> -rearranged with leukemic presentation and hemophagocytic lymphohistiocytosis
EA4HP26-LYWS-380	Peripheral T cell lymphoma, not otherwise specified, lymphoepithelial (Lennert) variant
EA4HP26-LYWS-388	2-year-old boy with ALK+ ALCL and secondary hemophagocytic lymphohistiocytosis
EA4HP26-LYWS-391	Challenging diagnosis of a nodal T follicular helper cell lymphoma NOS, with epithelioid granulomata and cytotoxic T-cell expansion
EA4HP26-LYWS-394	An atypical case of primary peripheral T cell lymphoma – NOS in a young patient presenting a genetic immunodeficiency.
EA4HP26-LYWS-395	T cell lymphoma with indolent clinical behaviour and variable, evolving histological features across consecutive biopsies.
EA4HP26-LYWS-403	Lennert Lymphoma: A Rare Variant of Peripheral T-Cell Lymphoma with a Unique Tumor Microenvironment
EA4HP26-LYWS-408	ALK1-negative anaplastic T-cell lymphoma with secondary hemophagocytic lymphohistiocytosis
EA4HP26-LYWS-416	Peripheral T-Cell Lymphoma (PTCL-NOS) with a Lennert-like Pattern in patient diagnosed with sarcoidosis
EA4HP26-LYWS-429	ALK-Negative Anaplastic Large Cell Lymphoma
EA4HP26-LYWS-437	Granulomatous inflammation with abundant Langhans giant cells mimicking infection in follicular helper T-cell lymphoma, angioimmunoblastic type.
EA4HP26-LYWS-452	Primary Nodal EBV-Positive T/NK-Cell Lymphoma with Hodgkin-Like features in an immunodeficient patient: A diagnostic challenge.
EA4HP26-LYWS-455	A case of an aggressive EBV positive peripheral T cell lymphoma with histiocytes showing hemophagocytosis in a patient with underlying immunodeficiency and HLH
EA4HP26-LYWS-456	Cytotoxic PTCL, NOS associated with hemophagocytic lymphohistiocytosis and harbouring a novel <i>VAV1::EVI5L</i> fusion

Splenic gamma-delta T cell lymphoma (non HSTCL) NOS with post splenectomy severe HLH

Dr. Shachar Naor

Sheba medical center, Pathology, Ramat-Gan, Israel

Case Description

64 yo woman with known long standing pancytopenia and splenomegaly (25cm) was admitted for further investigation. Prior BM biopsies showed no abnormal findings including flow, aspirate and OGM. On presentation a BMB in our hospital showed no abnormal findings including normal cellularity 50% and trilineage maturation. Moderate amount of interstitial non-atypical small T cells were seen on CD3, only rare scattered perforin and Granzyme-B positive cells, and polyclonal PCR study for TCR gamma. She developed recurrent fever. A splenectomy was performed.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No

Details of Microscopic Findings

The splenic red pulp was expanded with prominent erythrophagocytosis noted in the splenic cords. Focal areas in the red pulp cords showed clusters of large atypical lymphoid cells. The white pulp was preserved and non-affected. The hilum lymph node was normal. There was a patchy increase of gamma delta T cells (positive for TIA-1, perforin and Granzyme-B) in the red pulp (mainly in the cords, but also mild intrasinusoidal), including the atypical cells described above. Two weeks after the splenectomy she developed severe HLH clinical picture with severe pancytopenia and a repeated BM showed sheets of very atypical medium sized cells with the same immunophenotype as seen in the spleen and prominent hemophagocytosis.

Immunophenotype

The lymphoma cells were positive for CD3, gamma delta, TIA-1, perforin, Granzyme-B and negative for CD5, CD4, CD8 and CD7. The EBER-ISH, CD30, CD57 and CD56 were negative.

Cytogenetics

Only FISH for CEP8 was done on the spleen and showed monosomy in 40% of the cells.

Molecular Studies

TCR clonality on both gamma and beta PCR - same clones in the spleen and second BMB (polyclonal in the first BMB)

Oncomine NGS panel findings: CTLA4 SNV c.307T>C (VAF 48%) pathogenic, PDCD1LG2 SNV c.506C>T (VAF 44%) - VUS, DNMT3A INDEL (VAF 5.7%), TET2 INDEL (VAF 5.4%), BCOR SNV c.4596-1G>A (VAF 4.6%) pathogenic

Proposed Diagnosis

Splenic gamma-delta aggressive T cell lymphoma NOS (non HSTL) with severe HLH developing post-splenectomy.

Interesting Feature(s)

Primary splenic aggressive gamma delta T cell lymphoma NOS - not described before in the literature, associated with severe HLH which interestingly developed after splenectomy and was not present before the procedure. Background of long standing (at least 10 years) progressive splenomegaly and pancytopenia with no proof of obvious T-LGL clone in at least two bone marrow biopsies, and no other explanation.

Panel Diagnosis: Cytotoxic gd TCL with HLH (splenic? Non-HS)

Anaplastic Large Cell Lymphoma with Leukemic Relapse Misdiagnosed as Primary Hemophagocytic Lymphohistiocytosis

Dr. David Grier^{1,2}, Dr. Robert Lorsbach^{1,2}, Dr. Jingwei Li^{1,2}, Bethany Verkamp^{3,4}

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Case Description

A 15-year-old female presented to an outside hospital with a two-week history of fever (39°C), rash, and respiratory symptoms. Imaging revealed borderline splenomegaly and abdominal/chest wall tenderness. She was diagnosed with hemophagocytic lymphohistiocytosis (HLH) and started on HLH-94 protocol. Four months later, a lymph node biopsy revealed ALK-positive anaplastic large cell lymphoma (ALCL). Treatment had a good initial response. However, a repeat PET-CT shortly after discharge suggested relapse. One month later, she was admitted with body aches, fatigue, diarrhea, and severe headache. PET showed improvement of her ALCL. Laboratory findings included: sIL-2R: 4,189 U/mL and ferritin: >1,000,000 ng/mL. The suspected cause was recurrent HLH. No bone marrow biopsy was performed. She was transferred for management suspected relapsed HLH. Lab findings at CCHMC - CBC: WBC 7.61 K/mL, Hemoglobin 10.1 gm/dL, Hematocrit 30.6%, platelets 21 K/mL, C-reactive protein: 5.10 mg/dL (ref < 0.40), Lactate Dehydrogenase: 12,539 units/L (ref 100-325), Ferritin: 225.4 ng/mL (ref 8.0 -100), CXCL9: 1,155,233 pg/mL (ref < 647), Triglycerides: 769 mg/dL (ref 129), Fibrinogen: 99 mg/dL (ref 170-500), Soluble IL-2R: 11,724 U/mL (ref 137-838) The patient developed severe disseminated intravascular coagulation (DIC). Her condition progressed to multi-organ failure. Care was withdrawn and the patient passed away peacefully.

Biopsy Fixation Details

Not applicable

Frozen Tissue Available

None

Details of Microscopic Findings

Examination of the peripheral blood smear reveals 20% large atypical cells with ample cytoplasm, coarse cytoplasmic granules, large nucleoli, irregular nuclear contours, and coarse chromatin.

Immunophenotype

Flow cytometry revealed an abnormal T-cell population (26%) with increased side scatter that expresses CD30, variable CD8, CD7, CD2, CD56, HLA-DR, CD38, and CD45. They were negative for surface CD3, all and B-cell antigens.

Cytogenetics

Interphase FISH analysis utilizing DNA probes specifically flanking ALK (2p23) detected a rearrangement of ALK (2p23) in 32% of cells.

Molecular Studies

A HLH specific NGS panel revealed a mutation of *AP3D1* as a variant of undetermined significance (VUS).

Proposed Diagnosis

Leukemic relapse of ALK-positive anaplastic large cell lymphoma

Interesting Feature(s)

The patient was initially diagnosed with primary hemophagocytic lymphohistiocytosis (HLH), which delayed treatment for the underlying anaplastic large cell lymphoma (ALCL). She was transferred to our hospital for management of ARDS and HLH. ALCL was *not* believed to be the trigger of the HLH due to the reassuring PET scan. Malignancy-associated hemophagocytic lymphohistiocytosis (secondary HLH or S-HLH) presents a significant diagnostic challenge because its hallmark clinical and laboratory features primarily reflect severe hyperinflammation rather than

the underlying cause. In this context, cytopenias and systemic inflammatory findings can obscure an occult hematologic malignancy. Persistent or progressive disease despite standard HLH-directed therapy should prompt a comprehensive evaluation for an underlying malignancy. HLH should not be considered a single diagnosis but a constellation of laboratory and clinical findings, similar to shock or sepsis which do not define the underlying cause.

Panel Diagnosis: ALK+ ALCL in leukemic phase and with HLH

EA4HP26-LYWS-14

A Case of Lymphoepithelioid Variant of Peripheral T-cell lymphoma, NOS, in a 16-year-old Female

Dr. Anamarija Perry¹, Dr. Tamara Pikivaca², Dr. Robert Bell¹, Dr. Lina Shao¹

¹ University of Michigan, Department of Pathology, Ann Arbor, USA; ² University of Zagreb, Clinical Hospital Centre, Department of Pathology and Cytology, Zagreb, Croatia

Case Description

A 16-year-old female presented with approximately 2-year-history of abdominal pain, significant weight loss and diffuse lymphadenopathy. The excisional biopsy of the right femoral lymph node was done. PET staging showed multiple enlarged cervical, axillary, mediastinal, mesenteric, retroperitoneal, and inguinal lymph nodes with a maximum SUV of 3.1. The bone marrow and cerebrospinal fluid (CSF) were positive for involvement. The patient received chemotherapy and complete remission was achieved in the lymph nodes and central nervous system, but bone marrow showed residual disease. After receiving allogeneic bone marrow transplant, the patient achieved complete remission and remained lymphoma-free after 1.5 years of follow-up.

Biopsy Fixation Details

Formalin-fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections show a lymph node with completely effaced architecture by an atypical lymphoid proliferation in a diffuse growth pattern, composed of monotonous small to medium-sized lymphoid cells with irregular nuclear contours, clumped chromatin, inconspicuous nucleoli, and moderate amount of cytoplasm. There are numerous epithelioid histiocytes in clusters of variable size. Occasional eosinophils and plasma cells are admixed.

Immunophenotype

The lymphoma cells are positive for CD3, CD5, CD2, CD4, CD8 (subset), TIA1 (subset) and TCR BF1. The atypical lymphoid cells also show variable expression of ICOS and SAP, while they are negative for CD7, CD30, CD15, TCR delta, TCL1, CD34, TdT and CD1a. EBER shows rare positive cells.

Flow cytometry analysis of the lymph node, bone marrow aspirate and CSF revealed an atypical T- cell population positive for CD3, CD4, CD5, CD8 (partial), and CD45. These cells were negative for CD7. The aberrant T-cells had a monoclonal pattern of TRBC1 expression (TRBC1 negative).

Cytogenetics

Chromosomal analysis of the bone marrow aspirate revealed an abnormal mosaic female karyotype. The chromosome abnormality, t(4;16), observed in a single cell from the mitogen-stimulated culture (1 out of 30 analyzed cells), was consistent with an *IL2::TNFRSF17* fusion - 46,XX,t(4;16)(q25;p13.2)[1]/46,XX[12]

Chromosomal microarray analysis of the lymph node identified two variants with some clinical significance (Tier 2) in 70-80% of the cells: a loss of 759 kb at 4q27 including *IL2*, and a loss of 1.2 Mb at 16p13.13 including *TNFRSF17*.

Molecular Studies

T-cell rearrangement studies on lymph node, bone marrow and CSF all showed identical clonal T-cell population in all specimens.

NGS study (NCI - TruSight Oncology 500 Gene Panel v3; RNA Exome Fusion Panel v2.0) detected the *IL2-TNFRSF17* fusion with markedly elevated IL-2 expression. There was no evidence of pathogenic mutations.

Proposed Diagnosis

Peripheral T-cell lymphoma, NOS, lymphoepithelioid variant (Lennert lymphoma).

Interesting Feature(s)

We present a case of an adolescent female with stage IV PTCL, NOS with Lennert lymphoma morphology, involving CSF and bone marrow. Despite widespread disease the patient achieved complete remission after allogeneic BM transplant. PTCL, NOS occurs very rarely in children and adolescents with limited published data and no standardized treatment. The *IL2-TNFRSF17* fusion found in our patient's lymphoma is of uncertain clinical significance, but was previously described in at least one PTCL.

1. Laâbi Y, et al. EMBO J. 1992;11(11):3897-904.
2. Devine KJ, et al. Blood Adv. 2025. 25;9(6):1420-1431.

Panel Diagnosis: PTCL-NOS associated with granulomas, latter insufficiently florid for Lennert lymphoma

EA4HP26-LYWS-15

From skin lesion to bone marrow: T-cell lymphoma-NOS with prominent lymphohistiocytic infiltrate.

Dr. Elisa Lin, Dr. Kikkeri Naresh, Dr. Jason Love, Dr. Afshin Shameli, Dr. Alireza Torabi

University of Washington, seattle, Germany

Case Description

75 year old female with history of papillary thyroid carcinoma, intraductal carcinoma of left breast, presented with several skin lesions/nodules on her shoulder in 2018 as well as axillary adenopathy. The skin lesion was read as atypical dermal T-cell/histiocytic infiltrate (no biopsy from the lymph node). T-cell clonality showed a TCR gamma clonal population. Patient was treated with resolution of the skin lesions. In 2022 patient presented with pancytopenia and BM biopsy showed 20% involvement by abnormal CD4+ T-cell population and PET scan showed subcentimeter cervical adenopathy. She was treated with low dose methotrexate until 2024 when she presented with progressive lymphadenopathy; biopsy was compatible with PTCL-NOS. PTCL-NOS. She was enrolled in clinical trial but PET scan showed progression of the disease with progressive hyponatremia, neutropenia, fever and concern for HLH. Bone marrow biopsy was performed.

Biopsy Fixation Details

Punched biopsy of the skin lesions (2018), lymph node biopsy (2024) and bone marrow biopsy (2025) were fixed in formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

Skin biopsy (2018): Deep perivascular and periadnexal lymphohistiocytic infiltrate with predominantly small to medium sized lymphocytes and scattered larger lymphocytes are present.

Lymph node biopsy (2024): showed a diffuse lymphohistiocytic infiltrate. Histiocytes amount to >50% of the infiltrate, some with epithelioid features. Lymphoid cells include small reactive lymphocytes and medium to large sized atypical lymphoid cells with moderate amount of cytoplasm, irregular nuclear contours and small basophilic nucleoli. Diagnosis of T-cell lymphoma, NOS with prominent lymphohistiocytic infiltrate.

Bone marrow (2025): There are multifocal infiltrate of large neoplastic mononuclear cells with prominent nucleoli, and increased lymphocytes and histiocytes, consistent with involvement by T-cell lymphoma, NOS. Hemophagocytosis is present.

Immunophenotype

Skin: The majority of the lymphocytes are CD3+ T-cells, with a minor population of CD20+ B-cells. CD30 highlights scattered single cells, without significant clustering.

Lymph node: Most of the lymphoid cells are T cells. Larger atypical cells express CD45, CD2, CD3, CD5, CD4, BCL2 (weak), Granzyme B, TIA1 (rare), CD30 (a subset of larger cells), MUM1 (a subset), CXCL13 (a subset), and Ki67 (50%), and are negative for B-cell markers, CD7, CD8, CD10, BCL6, CD23, cyclin D1, CD15, EBER and light chains (kappa and lambda ISH). Smaller T cells retain expression of pan-T-cell markers and show CD4:CD8 ratio of ~2:1. Weak PD1 expression is seen in smaller lymphoid cells. Smaller lymphoid cells are positive for GATA3. CD21 and CD23 do not highlight any FDC meshworks.

Bone marrow: The large neoplastic cells (10-15% of the marrow cellularity) are positive for CD3, CD5 (dim), CD4, Granzyme B, and CD30 (variable from strong to dim), and negative for CD2, CD7, CD8, CD68, CD163, PAX-5, and EBER (ISH). TIA-1 appears positive in a minor subset.

Cytogenetics

N/A

Molecular Studies

Skin lesion: CLONAL T-cell receptor gamma gene rearrangement identified.

Lymph node: No clonal T-cell population identified. NGS was negative.

Proposed Diagnosis

T-cell lymphoma, NOS with prominent lymphohistiocytic proliferation.

Interesting Feature(s)

Skin lesion was the first presentation, although lymph node biopsy was NOT performed in 2018. The disease progressed to massive adenopathy, bone marrow involvement and eventually HLH. Neoplastic cells were CD4+ large T-cells with weak CD30 expression and cytotoxic markers in a background of many small lymphocytes and histiocytes.

Panel Diagnosis: PTCL-NOS with prominent histiocytic infiltrate

EA4HP26-LYWS-19

Nodal T-follicular helper cell lymphoma, angioimmunoblastic type, with granulomata

Dr. Betty Pui Kwan Chak

Royal Marsden Hospital, Histopathology, London, UK

Case Description

A 46-year-old man presented with fever, anemia, and generalized lymphadenopathy. PET-CT demonstrated widespread nodal disease above and below the diaphragm with multiple extranodal deposits involving retroperitoneal, peritoneal/serosal, subcutaneous, intermuscular sites, spleen and bone marrow. Initial core biopsies of left neck and groin lymph nodes in November and December 2024 was reported as granulomatous inflammation by referring hospital. A subsequent right neck lymph node excision biopsy in December 2024 confirmed nodal T-follicular helper cell lymphoma, angioimmunoblastic type, with associated granulomatous inflammation. He initially received CHOP, escalated to CHOP plus etoposide due to cytopenias, and subsequently four cycles of GDP chemotherapy for progressive disease. He is currently on Brentuximab for persistent disease. Latest left neck lymph

node core biopsy confirmed persistent disease and latest PET-CT showed progressive nodal and extranodal lymphomatous disease.

Biopsy Fixation Details

All specimens were fixed in formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

The lymph node was extensively replaced by small, poorly formed non-necrotizing epithelioid granulomata. Residual lymphoid tissue included small lymphocytes, scattered eosinophils, plasma cells, and occasional medium- to large-sized lymphoid cells with nuclear atypia, increased mitoses, and apoptotic bodies.

Immunophenotype

Most lymphocytes were CD3-positive T-cells. The medium- to large-sized cells were CD4-positive, expressing CD10, PD-1, ICOS, and CXCL13. CD2 and CD5 were retained. CD7 expression was lost. There was patchy CD30 expression. EBER and CD25 were negative. CD21 highlighted expanded follicular dendritic cell meshworks.

Cytogenetics

Not done.

Molecular Studies

Clonal TRB/TRG rearrangements were present. IGH/IGK rearrangements were polyclonal. Two TET2 likely pathogenic variants (c.1903C>T p.[Gln635Ter] and c.4018del p.[Ala1341HisfsTer22]) were detected at ~12% VAF.

Proposed Diagnosis

Nodal T-follicular helper cell lymphoma, angioimmunoblastic type, with granulomata.

Interesting Feature(s)

This case illustrates AITL with florid granulomatous inflammation masking neoplastic cells, initially misdiagnosed as granulomatous inflammation on core biopsy by referring hospital. Granulomata in TFH lymphomas reflect reactive microenvironmental changes rather than a distinct prognostic subset. Cytokine-driven immune activation can mimic reactive or infectious lymphadenitis. Published series indicate no consistent survival difference compared with conventional AITL, but granulomatous presentations may delay diagnosis. Careful cytologic and immunophenotypic assessment, with a low threshold for extended TFH marker studies and a high index of suspicion, is essential to avoid missed diagnosis. Early recognition has clinical and therapeutic implications in this aggressive lymphoma.

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-23

Synchronous T-follicular helper cell lymphoma (TFHL), NOS with Lennert-like features and TFHL, angioimmunoblastic type with identical clonality

Dr. Kennosuke Karube¹, Dr. Masafumi Suzuki²

¹ Graduate School of Medicine, Nagoya University, Department of Pathology and Laboratory Medicine, Nagoya, Japan; ² Chibanishi General Hospital, Department of Pathology, Matsudo, Japan

Case Description

A 83-year old male presented with an enlarged axillary lymph node. Computed tomography revealed several enlarged axillary nodes with the maximum size of 4.1cm. No other lymphadenopathy was identified. An excisional biopsy was performed for the axillary nodes. As a conclusive pathological diagnosis for the first biopsy was not given, the second biopsy was done for another enlarged node.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph nodes: One node showed that granulomatous components effacing the normal architecture, especially paracortex, preserving several regressed follicles. Various inflammatory cells including eosinophils and lymphocytes were intermingled in the granulomatous components. Medium-sized atypical lymphoid cells were scattered in and around the granulomatous components. HRS-like giant cells were not obvious. Another node showed a polymorphous infiltrate including small lymphocytes, immunoblasts, plasma cells, histiocytes, and eosinophils with hyperplastic high endothelial venules. Medium-sized atypical lymphoid cells with clear cytoplasm were scattered or identified as small clusters.

Immunophenotype

In one lymph node, immunostaining for CD68 highlighted the granulomatous component. The atypical medium-sized lymphoid cells were positive for CD3, CD4, PD1, and ICOS, consistent with a T-follicular helper (TFH) phenotype. A small number of medium-sized to large lymphoid cells positive for in situ hybridization for EBV-encoded small RNAs (EBER) were scattered throughout the lesion. No expansion of follicular dendritic cell (FDC) meshworks was observed with immunostaining for CD21 and CD23.

In another nodal lesion, the medium-sized atypical lymphoid cells also showed a TFH phenotype, accompanied by scattered EBER-positive cells. In contrast to the first lesion, expansion of FDC meshworks was demonstrated by immunohistochemistry for CD21 and CD23. CD68-positive histiocytes were scattered but did not form a distinct granulomatous pattern.

Cytogenetics

(1st nodal lesion) 48,XY, add(3)(p25), +2mar [4]/ 46, XY[14]

Molecular Studies

PCR for TCR-gamma (BIOMED2 protocol): identical monoclonal peaks were identified in the both lesions

Proposed Diagnosis

- (1) T-follicular helper cell lymphoma (TFHL), NOS with prominent granulomatous reaction
- (2) TFHL, angioimmunoblastic type

Interesting Feature(s)

Lennert lymphoma (LeL) is a epithelioid-rich variant of PTCL, whereas TFHL may occasionally present with similar morphology, creating uncertainty about the relationship between LeL-like TFHL and TFHL with angioimmunoblastic features (TFHL-AI). We encountered an 83-year-old man with axillary lymphadenopathy in whom two nodal lesions were biopsied: one displaying LeL-like morphology and the other showing typical TFHL-AI features. Both lesions expressed TFH markers and shared an identical TCR clone, demonstrating a common clonal origin. This case, the first report of synchronous LeL-like TFHL and TFHL-AI, provides direct evidence that these morphological patterns lie within the TFHL spectrum rather than representing authentic LeL. The recognition of granulomatous features is diagnostically useful, as granulomas in TFHL are irregular and polymorphic compared with the more uniform granulomas of true Lennert lymphoma. Together, these findings refine the understanding of TFHL heterogeneity and highlight the importance of integrating morphology, immunophenotype, and clonality for accurate classification.

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

Lennert lymphoma with a genetic profile

Dr. Kennosuke Karube¹, Dr. Kiyohisa Okamoto²

¹ Graduate School of Medicine, Nagoya University, Department of Pathology and Laboratory Medicine, Nagoya, Japan; ² Takayama Red Cross Hospital, Department of Pathology, Takayama, Japan

Case Description

A 70-year-old male presented with cervical mass. No generalized lymphadenopathy and B-symptom was observed. The cervical mass was excised.

Laboratory data:

WBC 4950/ml (no atypical cells), Hb 14.4 g/dl, LD 167 U/l, sIL2R 404 U/ml (normal range, 121-613), CRP 0.10 mg/dl

Imaging:

PET/CT revealed no abnormal FDG uptake in any sites other than the cervical mass.

Clinical course:

The patient was treated with CHOP chemotherapy followed by radiotherapy and achieved complete remission 42 months after diagnosis.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The lymph node architecture was completely effaced by numerous clusters of epithelioid histiocytes admixed with medium-sized lymphoid cells. The lymphoid cells showed a relatively monotonous morphology with mildly irregular nuclei and scant cytoplasm. Inflammatory infiltrates such as eosinophils and plasma cells were inconspicuous. Neither proliferation of high endothelial venules nor foci of follicular hyperplasia were observed. Hodgkin and Reed–Sternberg–like cells with prominent nucleoli or multinucleation were not apparent.

Immunophenotype

The medium-sized lymphoid cells were positive for **CD3**, **CD5**, **TIA-1**, and **TCR-β**, weakly positive for **PD-1**, and negative for **CD7**, **CD4**, **CD8**, **granzyme B**, **TCR-δ**, **ICOS**, **BCL6**, **CXCL13**, **perforin**, and **EBER-ISH**. No Hodgkin and Reed–Sternberg–like cells positive for **CD30** and/or **CD15** were identified. **EBER-ISH** did not reveal any positive cells within the specimen.

Flow cytometric analysis demonstrated an **abnormal T-cell population** characterized by **CD3⁺CD5⁺CD4[−]CD8[−]CD7[−]CD20^{dim}** immunophenotype.

Cytogenetics

Not evaluable

Molecular Studies

TRG rearrangement: monoclonal peak (+)

IGH rearrangement: polyclonal (FR1, FR2, FR3) Targeted panel sequencing identified several mutations, including PIK3R1 L449del (VAF, 20.5%) and HLA-DQA2 Q70K (19.8%), whereas no TFH-associated genetic alterations such as IDH2, RHOA, TET2, or DNMT3A were detected.

Proposed Diagnosis

Peripheral T-cell lymphoma, NOS (Lennert lymphoma)

Interesting Feature(s)

Lennert lymphoma is a rare morphological variant of **peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)**, characterized by numerous epithelioid histiocytes that mimic granulomatous inflammation and often obscure the neoplastic T cells. The tumor cells are typically small to medium-sized with mildly irregular nuclei and show a **non-activated cytotoxic phenotype** (TIA-1⁺, granzyme B[−]), expressing either **CD4** or **CD8**.

“Lennert-like” features, in which epithelioid granulomas are formed, may occasionally be observed in other lymphomas, including **B-cell lymphomas**. An important differential diagnosis is **nodal T follicular helper (TFH) cell lymphoma**, as lymphomas with lymphoepithelioid morphology and TFH immunophenotype should be classified in that category rather than PTCL-NOS.

Because of the rarity of Lennert lymphoma and the difficulty in differentiating it from other type lymphomas, there have been **no comprehensive reports describing detailed molecular features**, including **gene expression** and **mutation profiles**. The present case represents the **first report** to analyze the **mutation profile** of Lennert lymphoma.

Panel Diagnosis: PTCL-NOS lymphoepithelioid variant (Lennert lymphoma)

EA4HP26-LYWS-33

Atypical Clonal CD4-positive T-cell Infiltrate in a Patient with an Isolated Sinus Cavity Mass

Dr. Huma Asif, **Dr. Meredith Nichols**

Cleveland Clinic, Pathology and Laboratory Medicine, Cleveland, USA

Case Description

A 74-year-old female presented with double vision and blurred vision. Imaging demonstrated an infiltrative mass involving the skull base and sphenoid cavity with extension into the orbital apices, right pterygopalatine fossa, and bilateral cavernous sinuses. A biopsy of the mass demonstrated lymphoid stroma with foreign body giant cell reaction and polarizable material. Subsequent endoscopic skull base surgery with excision of the mass demonstrated a clonal CD4-positive T-cell proliferation with a robust histiocytic background. Imaging was negative for lymphadenopathy or other masses. Cerebrospinal fluid (CSF) flow cytometry demonstrated unremarkable T cells with polytypic TRBC1 expression, but T-cell lymphoma next-generation sequencing studies performed on the CSF demonstrated multiple pathogenic DNA variants and low-level *NUP214::ABL1* fusion. A bone marrow biopsy was normocellular with trilineage hematopoiesis. The patient was given corticosteroids and received radiation therapy to the skull base, with subsequent stabilization of her vision. There is no sign of progression of disease ten months after diagnosis.

Biopsy Fixation Details

The specimen was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

Sections demonstrated a relatively bland lymphohistiocytic infiltrate composed of small lymphocytes with mature chromatin, slightly irregular nuclear contours, and scant amounts of cytoplasm. Sinonasal epithelium was unremarkable. Poorly-developed granulomas were seen.

Immunophenotype

By immunohistochemistry, T cells expressed CD2, CD3, CD4, CD5, CD99, PD1 (subset), and ICOS (subset) and were negative for CD8, TIA1, granzyme B, BCL6, CD10, CXCL13, TCL-1a, CD56, CD30, ALK1, TdT, CD34, CD1a, LMO2, CL-NOTCH1, and EBER. Follicular dendritic cell meshworks were not expanded. The Ki67 proliferation index was 20-30%. AFB Fite and GMS stains were negative. Flow cytometry demonstrated an abnormal CD4-positive T-cell population with diminished expression of CD7 and monotypic TRBC1 expression.

Cytogenetics

Not performed.

Molecular Studies

Excisional biopsy:

T-cell clonality studies by PCR were positive for clonal rearrangements in TCR beta and gamma loci. T-cell lymphoma next-generation sequencing studies demonstrated *DNMT3A* p.Ala449Valfs*25 (VAF 34%), and the following variants of uncertain significance: *JAK3* p.Thr75= (VAF 48%), *TET2* p.Ile1177Ser (VAF 34%), and *TET2* p.Cys1289Tyr (VAF 32%). A hematologic fusion panel was negative. Universal bacterial, fungal, and AFB PCR was negative.

CSF: "Low-level" mutations in *TET2*, *DNMT3A*, and *KRAS*; "low level" del(9)(q34)*NUP214::ABL1* fusion.

Proposed Diagnosis

Atypical clonal CD4-positive T-cell infiltrate.

Interesting Feature(s)

Despite evidence of clonality, the T cells were cytologically bland, appeared mature, and had no overt immunophenotypic evidence of aberrancy aside from diminished CD7 expression. There was no evidence of infection despite numerous histiocytes. Extensive molecular testing of the sinus tumor demonstrated non-specific mutations that can be seen in both T-cell lymphomas and clonal hematopoiesis of indeterminate potential. The significance of the low-level fusion seen in the CSF is unclear and raises the possibility of overinterpretation of "noise" of the assay; limited technical information about this assay is available. This case was discussed extensively at multiple consensus conferences and tumor boards, as it challenges the boundary of a very unusual reactive process versus an unusual presentation of an indolent lymphoma.

Panel Diagnosis: PTCL-NOS

EA4HP26-LYWS-34

Hemophagocytic lymphohistiocytosis associated with a primary bone marrow peripheral T-cell lymphoma mimics EBV-negative aggressive NK cell leukemia

Jinjun Cheng, Natasha Lewis, Fiona Craig

Mayo Clinic Arizona, Laboratory Medicine and Pathology, Phoenix, USA

Case Description

A 53-year-old Asian male with a history of hypertension, borderline diabetes on metformin, who presented several weeks of fatigue, fevers, night sweats, and weight loss. A PET-CT scan was unremarkable; No lymphadenopathy, no splenomegaly, and no liver or gastrointestinal lesions seen. Laboratory workup (pancytopenia, elevated ferritin >40K, fever, elevated triglycerides, elevated IL2 receptor) were consistent with hemophagocytic lymphohistiocytosis (HLH). Bone marrow biopsy at outside hospital was concerning for a lymphoid malignancy. Patient referred to Mayo Clinic Arizona and a bone marrow biopsy was repeated.

Biopsy Fixation Details

Formalin-fixed, paraffin embedded tissue, stained with hematoxylin and eosin as well as additional immunohistochemical stains

Frozen Tissue Available

None

Details of Microscopic Findings

Bone marrow biopsy shows hypocellularity with interstitial infiltrate of abnormal lymphoid cells and occasional hemophagocytosis.

Immunophenotype

The bone marrow biopsy demonstrates a patchy and interstitial infiltrate of abnormal lymphoid cells with a mature cytotoxic T-cell immunophenotype: CD3 positive, CD8 positive, CD56 positive, BF1 (TCR alpha-beta) positive, TIA-1 positive, granzyme B positive, CD30 rarely positive. TCR-delta, CD4, CD5, CD103, and EBER are negative. Kappa and lambda shows scattered polytypic plasma cells.

Flow cytometric immunophenotypic analysis identified an aberrant T cell population that represents about 44% of the total analyzed white blood cells and shows the following immunophenotype: CD45+, CD3+, CD8+, CD56+, CD7 dim+, CD2+; Negative with CD4-, CD5-, CD57-, CD34-, TdT-, CD117-, and TRBC1-. CD16 appears to be dimly positive on aberrant T cells.

Cytogenetics

Karyotype 46,XY[7]

Result: nuc ish(5q35; TLX3,BCL11B)x3[30/200],(14q11.2; TRADx3; 14q32; BCL11Bx3) [12/100]

Molecular Studies

Pathogenic Mutations Detected by Next Generation sequencing panel:

1. DDX3X: Chr X(GRCh37):g.41205842C>T; NM_001356.4(DDX3X):c.1582C>T; p.Arg528Cys (8%)
2. STAT3: Chr17(GRCh37):g.40475058C>G; NM_139276.2(STAT3):c.1852G>C; p.Gly618Arg (18%)
3. TET2: Chr4(GRCh37):g.106157646_106157650del; NM_001127208.2(TET2):c.2547_2551del; p.His850* (16%)
Chr4(GRCh37):g.106190867A>G; NM_001127208.2(TET2):c.4145A>G; p.His1382Arg (16%)

Bone marrow, T-cell receptor gene rearrangement analysis:

Positive. Clonal T-cell receptor gene rearrangement was detected.

Proposed Diagnosis

Peripheral T-cell lymphoma, not otherwise specified.

Interesting Feature(s)

Peripheral T-cell lymphoma with cytotoxic phenotype and concurrent HLH can exhibit an aggressive clinical course and poor prognosis.

The clinical presentation, morphology, cytotoxic immunophenotype, genetic mutations, and patient outcome of this PTCL,NOS case closely mimic those of EBV-negative aggressive NK cell leukemia.

Panel Diagnosis: Cytotoxic PTCL involving bone marrow

EA4HP26-LYWS-42

Nodal CD4+ T-cell lymphoma with Lennert-like morphology, incomplete TFH immunophenotype and molecular findings suggestive of nodal T follicular helper cell lymphoma (nTFHL)

Dr. Gorana Gasljevic^{1,2}, PhD/MD Eva Erzar³, PhD/MD Vanesa S. Ivanova⁵, PhD/MD student Panna Dora¹, Prof. Veronika Kloboves Prevodnik^{4,2}, Prof. Stefan Dirnhofer⁵, Prof. Alexandar Tzankov⁵

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Case Description

75-yrs-old male, otherwise healthy. He has noticed enlarged lymph nodes (LNs) in both inguinal regions. He denied B symptoms. Clinical examination showed peripheral lymphadenopathy with LNs up to 2 cm on the neck, in both axillas and inguinal regions. Lab at the time of admission: Leu 8.8x10⁹/L, Hgb 136 g/L, Plt 275x10⁹/L, LDH 4.43 ukat/L (norm<4.13). CT showed lymphadenopathy at both aspects of the diaphragm. Bone marrow biopsy was positive

for lymphoma. Clinical stage was IVA, International prognostic index 3. He was treated by 8 cycles of modified CHOP from September 2008 until March 2009. No BM transplantation was performed. Complete remission was achieved. He was followed by regular clinical controls but experienced intractable disease relaps and passed away in April 2013.

Biopsy Fixation Details

10% buffered formalin overnight

Frozen Tissue Available

No

Details of Microscopic Findings

Diffusely effaced lymph node architecture. Diffuse proliferation of epithelioid histiocytes with relatively rare neoplastic cells that are small to medium sized, with slightly irregular nuclear contours. No FDC proliferation. No high endothelial venules proliferation. Besides, there are some reactive small lymphocytes with condensed chromatin and rare immunoblasts.

Immunophenotype

Neoplastic cells are positive for CD3, CD2, CD4, CD5, CD7, focally ICOS, PD-1, rare for CD10 and CXCL13, and negative for CD8, CD20, BCL6, CD30. Small reactive background lymphocytes are CD8/TIA-1/Granzyme B positive. Few immunoblasts are EBV-ISH positive.

Cytogenetics

NA

Molecular Studies Clonal TR (TCRB) gene rearrangement by PCR Biomed-2.

HTS showed mutations in *RHOA* p.Glu47Lys VAF 22%, *CREBBP* p.Arg413Ter VAF 20.31% and *DNMT3A* p.Arg891Trp VAF 3.9%

Proposed Diagnosis

Nodal CD4+ T-cell lymphoma with Lennert-like morphology, incomplete TFH immunophenotype and molecular findings suggestive of nodal T follicular helper cell lymphoma (nTFHL)

Interesting Feature(s)

This is a case of nodal CD4+ T cell lymphoma with a so called Lennert lymphoma-like morphology, and incomplete expression of TFH markers and substantial infiltration by accompanying cytotoxic T-cells. HTS revealed the presence of *RHOA* p.Glu47Lys, *CREBBP* p.Arg413Ter and *DNMT3A* p.Arg891Trp mutations. The combination of *RHOA* p.Gly17Val together with *TET2/DNMT3A/IDH2* mutations is considered highly characteristic of TFH-derived T-cell lymphomas. Although in our case non-canonical *RHOA* p.Glu47Lys is present, its co-occurrence with *DNMT3A* mutation together with a partial TFH immunophenotype points toward the diagnosis of nTFH with Lennert-like morphology. Non-AITL nTFHL tend to show a more incomplete TFH profile compared to nTFHL of AITL type. This case illustrates the necessity of integrative clinicopathological and molecular analyses in the diagnosis of nodal lymphomas of TFH origin. Additionally, this case exemplifies how neoplastic population may occasionally be obscured by cytotoxic T-cell expansions which could potentially lead to misdiagnosis.

Panel Diagnosis: nTFHL /TFHL-NOS

ALK+ anaplastic large cell lymphoma (ALK+ ALCL), lymphohistiocytic variant: widespread nodal and extranodal dissemination with associated macrophage activation syndrome (MAS)

Dr. Rosa Brand, Dr. Ingrid Simonitsch-Klupp

Medical University of Vienna, Dept. of Pathology, Vienna, Austria

Case Description

14-year-old male patient initially admitted with presumed febrile gastroenteritis and elevated CRP (~19 mg/ml)- No clinical response to IV antibiotics (amoxicillin/clavulanate, then piperacillin/tazobactam).
- MRI/CT and ophthalmologic evaluation revealed multi-organ infiltrations: lung, kidneys, adrenals, pancreas, liver, CNS, extraocular muscles, choroid, salivary glands; hilar/mediastinal lymphadenopathy.
- Supraclavicular lymph node biopsy performed; empiric treatment for suspected sarcoidosis with methylprednisolone (2×1 g) led to only transient fever improvement.
- Concern for early macrophage activation syndrome (MAS) → trametinib + anakinra therapy initiated;
- Clinical deterioration followed, particularly respiratory, with progressive interstitial infiltrates and pleural effusions;
- Bone marrow and effusion analysis revealed two abnormal cell populations: macrophage-like cells (compatible with MAS) and a second population with round nuclei and cytoplasmic protrusions (~6% of BM).

Biopsy Fixation Details

10% buffered formaline

Frozen Tissue Available

no

Details of Microscopic Findings

- Lymph node architecture completely effaced;
- Loose infiltrate composed predominantly of histiocytic cells with round to oval nuclei, partly resembling large purple macrophages (LPMs);
- Background small lymphocytes present;
- *Key findings:* Scattered large atypical lymphoid cells, mostly singly distributed but also in perivascular groups with irregular, eccentrically located, often folded or indented nuclei with prominent nucleoli; cytoplasm narrow to moderately broad, variably vacuolated or foamy.
- No cohesive sheets of atypical cells; instead intermixed with histiocytes and small lymphocytes

Immunophenotype

Lesional large atypical cells:

Strong, specific CD30 expression; CD2+, CD7+, TCR alpha+, MUM-1+, Perforin+, GB7+, TIA-1+, CD3+
Specific nuclear and cytoplasmic ALK-1 positivity
Negative for other T-cell (CD5, CD4, CD8) and B-cell (CD20, CD79a) markers

Background cells:

Mixed T-cells (CD3+, CD5+) and B-cells (CD20+, CD79a+)
Histiocytes strongly positive for CD68R, CD163, CD14
EBER in-situ hybridization negative
HHV-8 negative

Cytogenetics

n.d.

Molecular Studies

ALK-FISH positive (break apart probe) in tumor cells of pleural effusion

Proposed Diagnosis

ALK+ anaplastic large cell lymphoma (ALK+ ALCL), lymphohistiocytic variant; widespread nodal and extranodal dissemination with associated MAS.

Interesting Feature(s)

- Sparse neoplastic cells hidden in a dense histiocytic background
- The infiltrate is dominated by reactive histiocytes/macrophages, which may mimic: Hemophagocytic processes, Histiocytic disorders, Granulomatous inflammation
- > This makes the tumor easy to miss on routine histology
- Prominent histiocytic reaction: Histiocytes may appear atypical themselves, further complicating diagnosis
- Perivascular clustering of tumor cells: Hallmark ALCL cells tend to cluster around blood vessels; this contrasts with the usual cohesive sheets seen in the common type of ALCL
- Classical „hallmark cells“, but subtle --> contributing to misdiagnosis
- Strong ALK expression despite low tumor cell density; IHC essential (morphology alone is misleading)
- This ALCL variant shows a typical association with systemic inflammation (MAS)
- Potential confusion with Hemophagocytic Lymphohistiocytosis (HLH)
- Common diagnostic pitfalls: Reactive or infectious lymphadenitis, Histiocytic syndromes, Sarcoidosis, HLH/MAS without underlying malignancy

Panel Diagnosis: ALK+ ALCL, lymphohistiocytic variant and HLH

EA4HP26-LYWS-63

EBV-Positive Lymphoproliferative Disorder and Subsequent Follicular Helper T-Cell Lymphoma Share Identical Genetic Alterations

Dr. Ke Li, Dr. Liuyan Jiang, **Dr. Ji Yuan**

Mayo Clinic, Jacksonville, USA

Case Description

A 60-year-old man presented with a left parotid mass that had fluctuated in size for two years. CT scan revealed a 2.6 cm left parotid mass with associated lymphadenopathy. He underwent excision of a left postauricular lymph node **(A)** and a left parotid mass **(B)**. Postoperative imaging showed no lymphadenopathy. Seven months later, he developed diffuse lymphadenopathy and underwent an excision of a right neck mass **(C)**. He received CHOPx4 with progression, followed by R-GEMOX5 (mixed response) and ICE x2, but the disease persisted. He died 35 months after diagnosis.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

A. Sections of left postauricular lymph node reveal distorted architecture with irregular follicles lacking germinal centers. Interfollicular areas contain small mature lymphocytes, clusters of epithelioid histiocytes, and rare Hodgkin/Reed-Sternberg (HRS)-like cells.

B. Sections of left parotid mass show complete effacement by a diffuse, polymorphous infiltrate of small lymphocytes, eosinophils, histiocytes, and large immunoblasts.

C. Sections of right neck mass show marked interfollicular expansion by abundant epithelioid histiocytes, atypical small-to-intermediate lymphocytes, scattered large lymphocytes, plasma cells, and rare eosinophils.

Immunophenotype

Flow cytometry: **A and B.** No clonal B- or aberrant T-cell population. **C.** 10% atypical T cells (surface CD3–, CD4+, CD5+, CD8–).

Immunostaining: **A.** CD20 stains the distorted follicles and CD3 highlights small T-cells. HRS-like cells are positive for CD30, PAX-5 (weak) and EBER; and are negative for CD20. Plasma cells are polytypic by kappa/lambda ISH.

B. Large cells are positive for EBER, CD20, PAX-5, CD30 (partial), CD45, MUM1, BCL6, and MYC. EBER stains large and small lymphocytes. Plasma cells are polytypic by kappa/lambda ISH. CD3+ T cells include mixed CD4+ and CD8+ subsets.

C. The atypical lymphoid infiltrate is positive for CD3, CD4, CD5, CD7, BCL6, PD1, ICOS and CXCL13 (partial). EBER highlights rare positive lymphocytes. Plasma cells are polytypic by kappa/lambda ISH.

Cytogenetics

N/A.

Molecular Studies

Immunoglobulin gene rearrangements, PCR (**A, B, C**): Polyclonal. *T-cell receptor* gene rearrangement, PCR: **A and B** polyclonal; **C** clonal.

NGS (**B**): *RHOA* G17V (2%), *TET2* M1164fs62 (13%), *TET2* Q1348R (13%). (*BRCA2* not in the panel)

NGS (**C**): Same mutations as specimen B with *RHOA* G17V (3.5%) and *BRCA2* N1626fs12 (45%).

Proposed Diagnosis

A and B. Polymorphic EBV-positive lymphoproliferative disorder (EBV+ LPD). **C.** Follicular helper T-cell lymphoma (TFHL), NOS.

Interesting Feature(s)

EBV+ LPD shows a broad morphologic spectrum, with specimen A resembling lymphocyte-rich CHL and B showing a diffuse polymorphous EBV+ B-cell infiltrate, making the diagnosis challenging. EBV+ LPD and TFHL may occur concurrently or sequentially. Our cases demonstrate that they are clonally related, sharing CHIP-associated mutations (*TET2*) and acquiring additional genetic alterations (*RHOA*) that drive progression toward T-cell lymphoma. Although specimen B lacked the evidence of a T-cell clone by flow cytometry or *TCR* gene rearrangement, NGS identified an identical low-level *RHOA* mutation, indicating the presence of a small neoplastic T-cell infiltrate obscured by florid EBV+ B-cell proliferation. These findings highlight the diagnostic challenges of recognizing early TFHL.

Panel Diagnosis: A) further investigation needed, but likely nTFHL/TFHL + HRS-like cells (no material available); B)nTFHL/TFHL-NOS + 20 EBV+ polyclonal B-LPD; nTFHL-NOS

EA4HP26-LYWS-74

Lennert Lymphoma

Dr. Cuiping Zhang, Dr. Linnea Banker, Dr. Soumya Mikkilineni, Dr. Richard Hammer

University of Missouri Healthcare, Pathology and Anatomic Sciences, Columbia, Germany

Case Description

76-year-old man with a history of prostate cancer treated with radiation therapy, chronic kidney disease, hypertension, Grover's disease, and prior excision of an unknown skin cancer with an 18-month history of persistent generalized pruritus. Eight months before presentation, he developed intermittent night sweats and hot flashes with progressive right axillary lymphadenopathy. Infectious workup was negative. Ultrasound showed a markedly enlarged right axillary lymph node measuring 6.5 × 2.6 × 6.8 cm. PET/CT revealed multiple FDG-avid lymph nodes with involvement of the spleen and palatine and lingual tonsils. An initial lymph node core biopsy was suspicious for

lymphoma, with differential diagnoses including peripheral T-cell lymphoma and Hodgkin lymphoma, prompting excisional biopsy.

Biopsy Fixation Details

Excisional lymph node biopsy specimen was received fresh for lymphoma workup underwent fixation in B-Plus fixative for 2 hours, followed by transfer to formalin prior to routine histologic processing. A portion of the lymph node was submitted for flow cytometric evaluation in RPMI.

Frozen Tissue Available

Not performed.

Details of Microscopic Findings

Sections reveal effacement of the normal architecture by a paracortical infiltrate consisting of medium- to large-sized cells with pleomorphic nuclei, vesicular chromatin, prominent nucleoli, frequent mitoses admixed with numerous epithelioid histiocyte clusters. In the background, there are scattered Reed-Sternberg-like cells, eosinophils, occasional immunoblasts and fibrosis.

Immunophenotype

Immunohistochemistry showed atypical cells positive for CD3, CD8, dim CD4, cytotoxic markers (TIA-1, granzyme B), with a Ki-67 index of approximately 30–40%, and negative for B-cell markers; CD68 highlighted increased histiocytes.

Flow cytometry identified a phenotypically distinct CD4- positive T-cell population with dim surface CD3, bright cytoplasmic CD3, and loss of CD7 was identified (8.1%, green population). A phenotypically distinct TcR Gamma Delta T-cell population with loss of CD5 and CD7 expression was identified (12.5%, orange population). No monotypic B cell population or blast population was detected.

Cytogenetics

Not performed.

Molecular Studies

Clonal T-cell receptor gene rearrangement is positive. Immunoglobulin Gene Rearrangement is negative. T-cell lymphoma FISH is negative. No TP63 rearrangement was observed.

Proposed Diagnosis

Peripheral T-cell lymphoma with epithelioid histiocytes compatible with lymphoepithelioid variant (Lennert Lymphoma) (ICC 2022, WHO5).

Interesting Feature(s)

Lennert lymphoma is a rare variant of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and often mimics Hodgkin lymphoma and reactive inflammatory conditions. This case highlights several diagnostically notable features. Clinically, the patient presented with chronic generalized pruritus and delayed B symptoms, resulting in an 18-month delay to diagnosis and underscoring its indolent and misleading presentation. Histologically, the lymph node showed complete architectural effacement by a paracortical infiltrate of atypical T lymphocytes with prominent clusters of epithelioid histiocytes, scattered Reed–Sternberg–like cells, eosinophils, and fibrosis. The neoplastic cells demonstrated a rare CD4(dim)+/CD8+ dual-positive T-cells with partial cytotoxic marker expression by immunohistochemistry. Furthermore, absence of ALK and TFH markers, negative EBV studies, and clonal T-cell receptor gene rearrangement supported classification as lymphoepithelioid PTCL-NOS, expanding the recognized clinicopathologic spectrum of this entity.

Panel Diagnosis: PTCL-NOS lymphoepithelioid variant (Lennert lymphoma)

Lennert-like nodal EBV+ T- and NK-cell lymphoma

Prof. Kung-Chao Chang

National Cheng Kung University Hospital, Department of Pathology, Tainan, Taiwan

Case Description

A 67-year-old woman suffered from right neck swelling since 2025 June. There was tenderness but no fever, drenching night sweats, weight loss or pain. After medication, the swelling improved but persistent lymph node enlargement was noted on the imaging examination. The neck sonography showed multiple enlarged lymphadenopathies at bilateral neck, level II-V with the largest one being 3cm at right level V. A neck lymph node biopsy was performed in September 2025.

Biopsy Fixation Details

The resected lymph node was fixed in neutral formalin for 10 hours and then paraffin-embedded. H&E sections and immunohistochemical staining were performed by the standard protocol.

Frozen Tissue Available

Frozen tissue was not available.

Details of Microscopic Findings

Sections showed a lymph node partially effaced by dense infiltration of medium-sized to large lymphoid cells with many small epithelioid granulomas and some eosinophils. The lymphoid cells showed round or ovoid nuclei with moderate amount cytoplasm and coarse chromatin. There were focal proliferations of high-endothelial venules without coagulative necrosis or angiocentric pattern.

Immunophenotype

On immunohistochemistry, the atypical lymphoid cells were positive for CD3, CD8, granzyme B and TCR-βF1 stains, while negative for CD20, CD4, CD10, PD-1, CD25, CD30, CD56 and TCR-δ stains. The EBER in situ hybridization was positive on the T cells, consistent with tumor cells, as shown by EBER/CD3 and EBER/CD20 stains. The Ki-67 index was about 60%.

Cytogenetics

There were 2 clonal populations of abnormal cells from the tumor cells involving BM:

45~46,XX,add(3)(p25)[4],add(4)(q35)[4],add(6)(q?22) [2],der(6)add(6)(p22)dup(6)(q?14q?27)[3][cp8]/
46,XX,t(15;20)(p10;p10)[2]/92,XXXX[3]/46,XX[11]

Molecular Studies

TET2 loss-of-function mutation (NM_001127208.2:p.T1066Lfs*16; c.3196delA; VAF, 20.8%)

Proposed Diagnosis

Primary nodal EBV+ T- and NK-cell lymphoma

Interesting Feature(s)

The presence of many small epithelioid granulomas may raise the possibility of Lennert's lymphoma.

Panel Diagnosis: EBV-positive nodal T-and NK-cell lymphoma

Extranodal ALK Positive Anaplastic Large Cell Lymphoma with Rare Fusion Partner and Fulminant Course Complicated by Hemophagocytic Lymphohistiocytosis

Dr. James R. Cook, Dr. Genevieve M. Crane

Cleveland Clinic, Pathology and Laboratory Medicine, Cleveland, USA

Case Description

A 52 year old man with history of ITP presented with progressive fatigue, chest pain, shortness of breath and weight loss. Imaging showed splenomegaly and signs of congestive heart failure. Initial work up of blood and bone marrow showed pancytopenia, IgG λ MGUS, and a small CD8+ T-cell population with monotypic TRBC1 by flow cytometry suggesting a possible T-LGL proliferation.

The patient was initially managed conservatively. After six months, the patient developed recurrent fevers and was treated with IVIG and prednisone for possible LGL leukemia, although diagnostic criteria were not met. Despite initial improvement in symptoms, by 15 months after initial presentation the patient experienced recurrent high grade fevers with pancytopenia, elevated IL2R and ferritin levels, and pancytopenia. The patient met criteria for hemophagocytic lymphohistiocytosis (HLH) at this time. Infectious workup was non-revealing.

Indurated skin lesions developed in the left flank and right buttock. CT/PET studies showed avid subcutaneous lesions with no nodal disease. Skin biopsy demonstrated an ALK positive ALCL that coexpressed CD8 and cytotoxic protein. Low level bone marrow involvement was identified on retrospective review, and a colon biopsy for GI bleeding showed focal ALCL. The patient continued on a fulminant course despite multiple therapies and passed away due to complications ~18 months following initial presentation.

Biopsy Fixation Details

Skin: FFPE

Frozen Tissue Available

N/A

Details of Microscopic Findings

Skin: Atypical lymphohistiocytic infiltrate involving subdermis, deep and superficial dermis. Mixture of histiocytes, small, mature lymphocytes, and large atypical cells with moderate to abundant cytoplasm and prominent nucleoli

Bone marrow: Slightly hypercellular bone marrow with trilineage hematopoiesis, focal lymphoid aggregates, no definite increase in plasma cells or dysplasia; large atypical forms best seen by IHC.

Colon: Focal, partially pervascular aggregates of atypical cells in lamina propria.

Immunophenotype

By IHC (skin, colon) and/or flow cytometry (BM):

Positive: CD3, CD8, CD30, MUM1, granzyme B, perforin, ALK (D5F3)

Negative: CD4, CD5, CD7, ALK1

Cytogenetics

Earliest available bone marrow biopsy: 46,XY,+1,add(1)(p12),t(1;2)(q12;q11.2),add(9)(p24)[3]/46,XY[17]

Subsequent karyotypes showed similar findings with increasing complexity (see PDF file).

Molecular Studies

PCR studies: Skin and PB positive for clonal T-cell population with similar amplicons

NGS studies of bone marrow:

RNA: *IRF2BP2::ALK* t(1;2)(q42.3;p23.2) IRF2BP2: exon 1 (NM_182972.2) ALK: exon 20 (NM_004304.5)

DNA: TP53 p.R175H, NM_000546.5, c.524G>A VAF: 9.4%

Proposed Diagnosis

ALK positive anaplastic large cell lymphoma involving bone marrow, skin and colon without evidence of nodal disease, complicated by HLH.

Background IgG λ MGUS

Interesting Feature(s)

- Unusual extranodal presentation of ALK positive anaplastic large cell lymphoma with fatal HLH
- Subtle bone marrow involvement recognized only via retrospective IHC, causing diagnostic challenges with CD8 positive T-cell population initially interpreted as possible T-LGL proliferation
- ALK protein detected by ALK1 D5F3 and not by ALK1 IHC
- *IRF2BP2::ALK* fusion previously reported only once in a pulmonary carcinoma

Panel Diagnosis: Extranodal ALK+ ALCL with HLH

EA4HP26-LYWS-80

CD4-Positive Lymphoepithelioid Lymphoma (CD4+ Lennert Lymphoma): An entity probably lying within the spectrum of nodal TFH lymphomas

Dr. Jagmohan S. Sidhu

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Case Description

In 8/2022, a 70-year-old male presented with dyspnea, bilateral pleural effusions & iatrogenic Cushing syndrome due to long-term high-dose corticosteroid use for sarcoidosis that was diagnosed in a cervical lymph node (LN) biopsy in 10/2021 at another hospital when his CT scan showed mediastinal, axillary & cervical lymphadenopathy (LAP). Repeat PET/CT in 8/2022 showed regression of previous LAP, but showed new subcarinal & retroperitoneal LAP, & right lung mass. Review of previous LN biopsy showed lymphoepithelioid lymphoma (LeL), not sarcoidosis. Thoracentesis specimen, fine needle aspirates of right lung mass & mediastinal LNs and bone marrow (BM) showed a few TFH cells. He received 6 cycles of brentuximab + CHP with a good complete response. He was too weak for a BM transplant. Follow-up PET/CT scans from 11/2024 to 8/2025 showed multiple bilateral pulmonary nodules increasing from 12 mm to 21mm in maximum size. Mesenteric/ iliac LAP was also noted in 8/ 25 PET/CT. Lung biopsy of a right upper lobe lung nodule showed recurrent LeL. He recently completed 3rd of 8 planned cycles of gemcitabine + vinorelbine chemotherapy & a post 3rd cycle PET/CT showed no metabolic activity in the body.

Biopsy Fixation Details

10% neutral buffered formaldehyde

Frozen Tissue Available

Not available

Details of Microscopic Findings

H&E sections show complete effacement of architecture by a diffuse infiltrate of small lymphocytes with irregular nuclear contours & aggregates of bland histiocytes. A few mitoses are noted.

Immunophenotype

Immunohistochemistry: Small lymphocytes (SLs) are +ve for CD45, CD2, CD3, CD4, CD5, GATA3 (subset), TBX21 (subset), BCL2, and Ki67 (~40%). Variably sized small subsets of SLs are +ve for CD7, CD8, TIA-1, Granzyme B, perforin, PD1, ICOS-1, CXCL13, BCL6, CD10, CD20, CD31, & PAX5. CD138 shows a few plasma cells. EBV-LMP1 stains a few cells & CD30 stains a few activated cells. CD21 & CD23 highlight expanded irregular follicular dendritic cell (FDC) networks. Numerous histiocyte clusters stain for CD68.

Cytogenetics

Not done

Molecular Studies

In situ Hybridization: Polytypic plasma cells & a few EBER +ve cells

T and B Cell Clonality Studies: TCR beta & TCR gamma rearrangements detected (multiple peaks); both IGH & IGK rearrangements also detected.

DNA NGS (128 Genes): 2 *TET2* mutations [Q1526* (19.2% VAF) & I1873T (8.7% VAF)]

Proposed Diagnosis

CD4-Positive Lymphoepithelioid Lymphoma (CD4+ Lennert Lymphoma)

Interesting Feature(s)

1. **CD4+, instead of CD8+, LeL:** A preprint of 6 cases of CD4+ LeL mentions that CD4+ LeLs probably lie within the spectrum of nTFH lymphomas, usually express PD1 & ICOS and often have *TET2* mutation(s) (<http://dx.doi.org/10.2139/ssrn.4127746> or (<https://ssrn.com/abstract=4127746>). Our case has these features. Also, like nTFH of AITL-type, both T-cell & B-cell clonalities are +ve. Expanded CD21+/CD23+ FDC networks in our case look like those in nTFH lymphomas.
2. **Admixture of TFH-like cells & cytotoxic T cells in LeL:** It can occur in LeLs (*Am J Surg Pathol.* 2016; 40:1249-1260)
3. **Detection of TCRG & TCRB multiclonality:** 63% PTCL cases showed multiple TCRB & TCRG rearrangements (indicating genetic instability of PTCLs) in a large study. (*Acta Naturae.* 2015;7:116-25).
4. **Admixture of GATA3+ & TBX21+ T cells:** It can occur in a lymphoma with admixture of TFH-like cells & cytotoxic CD4+T cells (*J Allergy Clin Immunol.* 2016;138: 825–838; *Front. Immunol.* 13:867189; *Front. Immunol.* 11:607626; *Cell Mol Immunol* (2021) 18:528–538).
5. **Behavior of our case is more aggressive than a usual LeL:** TFH marker +ve LeL behaves more aggressively than TFH marker-negative LeL (*Am J Surg Pathol* 2016;40:1249-60).

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-83

Lennert's lymphoma (lymphoepithelioid variant of peripheral T-cell lymphoma, NOS) mimicking reactive (granulomatous) lymphadenopathy

Stefan Dirnhofer

Universitätsspital Basel, Pathology, Basel, Switzerland

Case Description

71 yrs old male, otherwise healthy. Returned from 3 month vacation in Spain. He has noticed enlarged lymph nodes (LNs) in the neck. No B symptoms. Clinical examination showed peripheral lymphadenopathy with LNs up to 10 cm in the neck, both axillas and inguinal regions. Peripheral blood with normal values. LDH elevated: 350 U/L (norm<120). PET/CT showed generalized lymphadenopathy with bulky disease cervical. SUVmax was 17.5. No bone marrow biopsy was performed. Clinical stage was IIIA, bulky. He was treated with CHOP starting September 20025 and received a partial remission after 3 cycles.

Biopsy Fixation Details

Lymph node supraclavicular left, excisional biopsy, formalin - fixed, paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

Diffusely effaced lymph node architecture due to a proliferation of epithelioid histiocytes forming occasionally granuloma-like structures admixed with small to medium-sized atypical lymphoid. No high endothelial venules proliferation. No FDC proliferation.

Immunophenotype

The atypical cells are positive for CD2, CD3, CD4, CD5 and TCRBetaF1. They show loss of CD7 and negativity for ICOS, PD-1, CXCL13, CD8, CD30, TIA1, GrB, Perforin, TCL1 and TCRDelta. Small reactive background lymphocytes are CD20-positive B-cells. No demonstration of EBV (EBER).

Cytogenetics

None

Molecular Studies

TCRg - Rearrangement (NGS): clonal

NGS Lymphoma panel (172 genes): no pathogenic variant

Proposed Diagnosis

Peripheral T-cell lymphoma (PTCL), NOS

Lymphoepithelioid variant, so called Lennert's lymphoma

Interesting Feature(s)

This case is a histiocyte-rich variant of a peripheral T-cell lymphoma, NOS (Lennert's lymphoma). The numerous clusters of epithelioid histiocytes mask the underlying neoplastic process (small to medium-sized atypical T – cells) and raise the differential diagnosis of a reactive lymphadenopathy with epithelioid histiocytes (e.g. viral, drug-related or autoimmune).

The cytologic atypia, the loss of CD7, the demonstration of a clonal T-cell population by FCM and the clonal TCR-rearrangement by molecular analysis enable the diagnosis of a histiocyte-rich variant of a peripheral T-cell lymphoma, NOS (Lennert's lymphoma). However, no pathogenic variant could be demonstrated by a panel-sequencing.

Panel Diagnosis: PTCL-NOS lymphoepithelioid variant (Lennert lymphoma)

EA4HP26-LYWS-98

Indolent CD4 positive clonal T-cell lymphoproliferative disorder, EBV negative occurring in post-transplant setting

Dr. Ye L. Hock, Bindu Vydianath, Matthew Pugh

University Hospitals Birmingham NHS Trust, Cellular Pathology, Queen Elizabeth Hospital, Birmingham, UK

Case Description

A 72-year-old male, who had a renal transplant in 1994 for polycystic kidney disease with end stage renal failure, was noted to have mediastinal and massive para-aortic lymphadenopathy on CT scan. He was on Ciclosporin and mycophenolate as well as on Vendolizumab for Crohn's disease. EUS biopsy was performed (submitted). 2 skin lumps were also noted and excised (microphotos submitted) but he had no evidence of mycosis fungoides clinically. He was treated with CHOP and post-cycle 4 CT showed significant reduction in lymph node volumes but end of treatment (post-cycle 6) PET CT showed progressive nodal disease above and below diaphragm (SUV max 8.6) with peritoneal deposits. Needle biopsy of left inguinal lymph node was performed (photos submitted).

Biopsy Fixation Details

10% buffered formaldehyde

Frozen Tissue Available

No

Details of Microscopic Findings

Pre-treatment EUS and post-treatment lymph node biopsy show similar features with a rather similar lymphoid infiltrate in the skin as well. There is a diffuse infiltrate of small T-lymphoid cells with many scattered non-necrotizing epithelioid cell microgranulomata.

Immunophenotype

Positive: CD2, CD3, CD5, CD4 (CD4:CD8 >10:1), Beta F1

CD7: some loss (~50%)

Ki67: very low
Negative: CD30, PD1, CD10, BCL6, CD25, TdT, ALK, CD20, CD79a, Pax 5 (scant residual B cells), EBER, TCR delta, ZN, Fungal stain

Cytogenetics

Not performed

Molecular Studies

Genomic analysis (EuroClonality-NDC) on EUS lymph node biopsy:

KRAS variant [c.38G>A p.(Gly13Asp)], VAF 13%

Clonal TRA (TRAV8-1/TRAJ3, TRAV13-1/TRAJ29), TRB (TRBD1/TRBJ1-1, TRBV12-5/TRBJ2-3) & TRG (TRGV2/TRGJP1, TRGV8/TRGJP2) rearrangements.

Poor DNA quality in skin and post-CHOP lymph node biopsies

Proposed Diagnosis

CD4 positive clonal T-cell lymphoproliferative disorder, EBV negative occurring in post-transplant setting (histologically indolent)

Interesting Feature(s)

NK/T-cell lymphoproliferative disorders (LPD) occurring in post-transplant setting (PTLD) are rare and the majority represent PTCL, NOS. EBV negative PTLD and NK/T-cell PTLD tend to present late. In our patient, this T-cell LPD occurs 30 years post-transplant. Indolent T-LPD rarely present as primary lymph node disease and PTLD of indolent T-LPD subtype are exceptionally rare. Indolent CD4+ T-LPD usually presents in skin or gastro-intestinal tract. Clinical picture in our case excludes these possibilities. Epithelioid cell microgranulomata are well described in T-LPD, most commonly in association with Lennert lymphoma (PTCL, NOS). In the context of immunodeficiency, microgranulomata would raise the possibility of an infective aetiology. In our case, the presence of only small bland looking T-cell with abundant microgranulomata may mislead into the diagnosis of granulomatous lymphadenopathy such as sarcoidosis. Nevertheless, the clinical picture and molecular genetics confirm this to be a clonal T-LPD. Currently by WHO Haem5, such cases of indolent primary nodal T-LPD would fall under the category of PTCL, NOS but indolent T-LPDs generally do not respond to standard therapy for PTCL, NOS such as CHOP and may require a different therapeutic approach such as ciclosporine or methotrexate monotherapy. Hence, separate categorization of 'nodal indolent CD4 positive T-cell LPD' may be justified.

Panel Diagnosis: PTCL-NOS arising in ID/dysregulation

TCR-Silent Nodal Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL, NOS) with Malignancy-Associated Fulminant Hemophagocytic Lymphohistiocytosis (HLH)

Dr. Kedar V. Inamdar, Dr. Elizabeth Wey, Dr. Juan Gomez-Gelvez, Dr. Yulei Shen, Dr. Sharmila Ghosh, Dr. Wei Liu

Henry Ford Hospital, Pathology, Detroit, USA

Case Description

51-year-old man with no significant past history, presented with a 10-day onset of fever, chills, nausea, vomiting and diarrhea, and extreme fatigue. He reported 25-30 lb. weight loss in the past 3 weeks. Laboratory values at presentation showed pancytopenia (WBC 1.2 K/L, hemoglobin 11.4 g/dL, platelets 11K/uL), abnormal liver function tests (total bilirubin 4.8 mg/dL, SGPT 233 IU/L and SGOT 434 IU/L), acute renal failure and markedly elevated LDH (7597 IU/L), serum ferritin (104,458 ng/mL) and serum soluble IL2 receptor CD25 (11,850 pg/mL). Whole-body CT scan showed hepatosplenomegaly, and extensive lymphadenopathy. A bone marrow and left inguinal lymph node biopsy were performed.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph Node: Focal sheets of large, pleomorphic lymphoid cells with hyperchromatic nuclei distort the nodal architecture. Background shows frequent mitoses, apoptoses and significant necrosis. Focal hemophagocytosis (best visualized on CD68 immunostain) is seen.

Bone Marrow: The core biopsy shows an extensive interstitial infiltrate of atypical, medium-to-large, pleomorphic, cells associated with significant apoptosis, frequent mitoses and fulminant hemophagocytosis. Malignant cells have hyperchromatic irregular nuclei, inconspicuous nucleoli and amphophilic cytoplasm. Trilineage hematopoiesis is decreased.

Immunophenotype

Immunohistochemistry:

Lymph Node: The malignant cells are positive for CD45, CD43, CD2, MUM1, Myc and TIA1 and negative for cytokeratin, CD20, PAX5, CD3, CD4, CD5, CD7, CD8, CD10, CD30, CD56, TCR beta F1, TCR delta and EBV by ISH. CD68 highlights numerous histiocytes, some with hemophagocytosis.

Bone marrow: The malignant cells are positive for CD45, CD43, CD2, Oct2, Bcl2, MUM1, Myc and Ki-67 (>95%). They are negative for cytokeratin AE1/AE3, SOX10, TTF1, synaptophysin, chromogranin, CD99, CD20, PAX5, CD79a, CD1a, CD3, CD4, CD5, CD7, CD8, CD10, cyclin D1, Bcl6, CD30, CD34, CD56, CD71, TdT, CD117, MPO, hemoglobin, Factor 8, CD138, CD163, HHV8 and EBV (by ISH). CD163 highlights numerous hemophagocytic cells.

Flow cytometry: Negative for clonal B- or aberrant T-cells in lymph node and bone marrow.

Cytogenetics

Lymph node: not performed

Bone marrow:

Karyotype: Complex. 45~46,XY,der(1)ins(1;?)(q12;?),add(2)(q21),add(4)(q35),add(5)(q35), 7,del(8)(q22),add(9)(p24),-10,-11,add(11)(q23),del(12)(q13q24.1),-13,add(13)(q34),add(14)(q24),del(16)(q13),-17,add(18)(q23),+der(19)t(11;19)(q13;q13.1), +3~5mar[2]/45,sl,-19[3]/46,XY[6]

FISH: Not Performed

Molecular Studies

Lymph node and Bone marrow PCR: Positive for clonal T-cell receptor gene rearrangement

Bone marrow NGS: Myeloid sequencing panel did not show coding variants or copy number alterations

Proposed Diagnosis

TCR-Silent Nodal Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL, NOS) with Malignancy-Associated Fulminant Hemophagocytic Lymphohistiocytosis (HLH)

Interesting Feature(s)

The immunophenotype (sCD3-, CD2+, CD4-, CD8-, CD5-) overlaps with malignancies of natural-killer (NK) cell lineage (such as NK/T cell lymphoma or aggressive NK cell leukemia). The lack of CD56 expression, no evidence of EBV by ISH and a positive TCR gene rearrangement argues against these and supports peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). The absence of TCR- $\alpha\beta$ and TCR- $\gamma\delta$ expression by lymphoma cells is consistent with TCR-silent PTCL. It has been hypothesized that the defective cytotoxic activity of the malignant T-cells in TCR silent PTCL may contribute to the inability to properly regulate the immune response, leading to the development of HLH (PMID: 34458948).

Panel Diagnosis: PTCL-NOS with HLH

EA4HP26-LYWS-123

ALK-positive anaplastic large cell lymphoma in a patient status post CAR-T therapy for multiple myeloma

Prof. Shiyong Li¹, Prof. Jonathan Kaufman², Prof. David Jaye¹

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Case Description

68-year-old male with a history of refractory IgG kappa myeloma status post CAR-T therapy

CT showed extensive chest and abdominal lymphadenopathy as well as splenomegaly.

Excisional biopsy of the left axillary lymph node was performed.

Patient was treated with Cytosan empirically.

Due to rapid deterioration, treatment was changed to comfort care.

Patient expired shortly after transitioning to hospice care.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Sections of the left axillary lymph node show complete loss of the nodal architecture by atypical lymphoplasmacytoid cells and abundant histiocytoid cells with frequent mitotic figures. There is admixed smaller number of small lymphocytes, which together with the histiocytes imparts a lymphohistiocytoid background pattern.

Immunophenotype

Flow cytometric immunophenotyping shows a distinct cell population (20% of total sample) with high light scatter that expresses CD2 (dim), CD4, CD5 (bright), CD11c (dim), CD26 (bright), CD81 and CD45. They are negative for surface CD3, CD7, CD8, CD10, CD19, CD20, CD22, CD27, CD34, CD38, CD56, CD138, CD200, kappa and lambda. B cells are small and polytypic. Plasma cells are rare and are polytypic.

Immunohistochemical stains show the cells of interest positive for CD4, CD5, TIA1 (subset), MUM1, CD33, CD25, CD30 and ALK1. They are negative for CD2, CD3, CD8, CD20, CD33, CD34, CD43, CD45, CD79a, CD117,

CD123, CD138, CD163, PAX5, MPO, granzyme B, TCRgamma and TCRbeta. CD33 and CD163 stain the abundant histiocytes, some displaying dendritic processes. In situ hybridization for Epstein-Barr virus (EBER) is negative. In situ hybridization for kappa and lambda immunoglobulin light chain shows scant reactivity consistent with a polytypic pattern.

Cytogenetics

Not performed

Molecular Studies

Positive for monoclonal T-cell receptor gamma gene rearrangement

Negative for monoclonal IgH/IgK gene rearrangement

Proposed Diagnosis

ALK-positive anaplastic large cell lymphoma rich in histiocytes in a patient status post CAR-T therapy for multiple myeloma

Interesting Feature(s)

ALK-positive anaplastic large cell lymphoma is rare in older patients.

The lymphoma is rich in histiocytes, obscuring morphologic assessment.

Secondary primary malignancies including T-cell lymphomas have been reported in patients who have undergone CAR-T cell therapy, with very rare cases derived from the CAR-T product. A relationship of the current case to the infused CAR-T product has not been demonstrated.

Panel Diagnosis: ALK+ ALCL

EA4HP26-LYWS-127

T-cell lymphoma with prominent histiocytes

Dr. Maja Nilsson Fors

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Case Description

79-years old male with COPD and atrial fibrillation. •August 2024 Sepsis and lymphadenopathy in the abdomen on CT scan.

•September 2024 Biopsy from lymph node in the abdomen was inconclusive and lymph node excision was recommended.

•December 2024 PET-CT scan with increased metabolic activity in lymph nodes in the axilla, mediastinum, abdomen and the inguinal region.

•February 2025 Lymph node from the left axilla was excised.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

3 pieces of frozen tissue are available.

Details of Microscopic Findings

Extensive histiocytic infiltrate with small to middle sized lymphocytes and a few large atypical cells in the background.

No epithelioid granulomas.

No eosinophilia.

Immunophenotype

The lymphoid infiltrate is dominated by T-cells with positive staining for: CD3/CD5/CD2/CD7 with a dominance of CD4+ cells over CD8+ positive cells which is more visible in areas with a less pronounced histiocytic infiltrate.

Negative staining for: CD10/BCL6/ALK-1/EBER/CD30/PAX-5/CD15

Flow cytometry: 80% of the lymphocytes are T-cells. Among the T-cells there are 25% of a/b type with dimCD3 expression and strong CD5 with a fraction with CD4 expression and another fraction with double-negativity for CD4/CD8. Positive expression for CD2, heterogeneous and only partially positive expression for CD7 and negative expression for CD1a.

Cytogenetics

No cytogenetics were performed.

Molecular Studies

Monoclonal results for TCRB(Vb27 Jb2-1) and TCRG(Vg11 JgP1) with primer-based NGS clonality analysis(LymphoTrack).

Proposed Diagnosis

Highly suspicious for Peripheral T-cell lymphoma of lymphoepitheloid type(Lennert lymphoma).

Interesting Feature(s)

The morphology is difficult to interpret because of the extensive histiocytic infiltrate that masks the neoplastic T-cells which in turn are not highly atypical. The atypical immunophenotype found by flow cytometry could not easily be confirmed by immunohistochemistry but a monoclonal rearrangement of the TCR-genes was found with molecular studies.

Panel Diagnosis: PTCL, immunoprofile suspicious for underlying neoplastic TFH population, but lack of specific markers and failed NGS precludes diagnosis.

EA4HP26-LYWS-132

Lennert lymphoma GATA3+

Dr. Sulaf Abd Own¹, Prof. Birgitta Sander¹, PhD/MD Anna Kwiecinska¹, Dr. Sulaf Abd Own²

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Case Description

A 40-year-old essentially healthy woman, with no B symptoms, was selected from breast screening due to enlarged lymph nodes in the axilla.

Mammography without any remarks in the breasts bilaterally, sparse glandular tissue without any suspicion of malignancy. Especially in the right axilla, asymmetrically thickened lymph nodes

In the depth of the right axilla, a slightly oblong lymph node measuring up to 4 cm is palpated; in the left axilla, there is no definite abnormality. In the right supraclavicular fossa, there is an approximately 1.5 cm large, rather rounded tumor.

Biopsy Fixation Details

Submandibular lymph node on the left side (T17478-25) measuring 30 x 18 x 15 mm. Two more biopsies, the largest measuring 8 x 5 x 3 mm. Mode of fixation: standard 10% buffered formalin. The material has been embedded in four paraffin blocks.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Histologically, a disturbed basic structure of the lymph node is seen in all fractions. No follicles are detected. The background showing abundant histiocytes accompanied by plasma cells, eosinophils. Atypical medium size

lymphoid cells are present, some are popcorn-like or resembling Reed–Sternberg cells. Single atypical mitoses can also be identified.

Immunophenotype

The atypical medium-sized cells express positivity for CD3 with varying intensity and are also positive for CD2 and CD5 but lack CD7. A significant proportion of these cells are CD4+ but also CD8+ cells are present. The cells are also positive for BF1 and GATA3, TIA and partly Granzyme. No significant positive expression for PD1 or CXCL-13 is detected. A smaller proportion are TPX21+ and few ICOS-positive cells can be identified.

Single CD30-positive cells are detected. However, these are CD15 and PAX5 negative. EBER is negative.

Furthermore, increased frequency of CMYC or p53 expression is seen in the large cells. Proliferation is approximately 50%.

In the associated flow cytometric analysis: CD3-, CD4+, CD8-, CD5+ CD7-, CD2+, CD10 -and TCR Cb1-.

Bone marrowfinding

A very small subpopulation of T-cells (less than 0,05 %) show identical with the previously diagnosed lymphoma aberrant CD5-positive, CD3-negative, CD4-positive T-cell phenotype.

Cytogenetics

DNA isolated from a tissue biopsy was analysed using a targeted lymphoid panel. Pathogenic variants in the KLH6 and PAX5 genes have been detected.

Copy number analysis using the panel shows complex changes, including dup(3q), and losses at 7q, 9, 14, 18, and 11q, including loss of the ATM gene.

Note that all changes are estimated at 10-20%, suggesting the proportion of tumor cells was low. Thus, we cannot completely exclude minor clonal changes (such as loss of p53 or RB1, or variants in TET2, RHOA, or IDH2).

Molecular Studies

PCR shows clonal rearrangement of T-cell gamma receptor.

Proposed Diagnosis

PTCL-NOS, GATA3+ with Lennert lymphoma-like features.

Interesting Feature(s)

- Some cases of Lennert lymphoma are biologically related to PTCL-GATA3. Lennert lymphoma is typically TBX21-positive, and only a small number of GATA3-positive cases have been reported.
- Genetic complexity related to GATA3+ PTCL-NOS.

Panel Diagnosis: PTCL, low level underlying nTFHL/TFHL with an expanded abnormal cytotoxic CD8 positive T-cell population

EA4HP26-LYWS-137

Follicular Helper Cell T-cell Lymphoma, Angioimmunoblastic Type, with Prominent Histiocytic Infiltrate Including Multinucleated Giant Cells

Dr. James Fleming, Dr. Ellen McPhail, Dr. Rebecca King, Dr. Karen Rech, Dr. Angela Collie

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Case Description

A 73-year-old male with a presumed history of multicentric HHV8-negative Castleman disease diagnosed three years prior at an outside institution and treated with steroids and siltuximab, presented with worsening symptomatic lymphadenopathy. Imaging studies identified multiple enlarged, metabolically active lymph nodes. An excisional cervical lymph node biopsy was performed.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Histologic sections of the cervical lymph node demonstrate complete effacement of the nodal architecture by a lymphohistiocytic infiltrate comprised of histiocytic/spindled cells, atypical lymphocytes, small lymphocytes, eosinophils, and sparse foreign body-type multinucleated giant cells. The atypical lymphocytes are intermediate in size with small nucleoli and eosinophilic to clear cytoplasm.

Immunophenotype

The atypical lymphocytes are positive for CD2, CD3 (weak), CD4 (weak, variable), CD5, CD20 (weak, variable), CD45, CD279, CXCL13, ICOS, and IDH2-R172K. They are negative for CD7, CD8, CD10, PAX5, TCR-BetaF1, and TCR-delta. A dual CD3/TRBC1 staining pattern is supportive of clonality, with the weakly CD3-positive T-cell population showing uniform lack of TRBC1 expression. EBER and HHV8 are negative. The prominent histiocytic and multinucleated giant cells are positive for CD68 and PU.1. Other markers highlight background inflammatory cells with expected phenotypes.

Cytogenetics

N/A

Molecular Studies

T-cell gene rearrangement studies are suspicious for a clonal T-cell process in a polyclonal background. Next generation sequencing with a targeted T-cell lymphoma gene panel demonstrates three pathologic variants (*IDH2* R172K, VAF 4%; *RHOA* G17V, VAF 4%; *TET2* N916*, VAF 10%).

Proposed Diagnosis

Follicular helper T-cell lymphoma, angioimmunoblastic type (ICC 2022) / Nodal T-follicular helper cell lymphoma, angioimmunoblastic type (WHO 5)

Interesting Feature(s)

This case of follicular helper T-cell lymphoma (FHTCL) demonstrates a prominent histiocytic infiltrate that obscures the atypical T-cells of the lymphoma. The original biopsy specimen initially diagnosed as Castleman disease was subsequently re-reviewed at our institution and showed more typical morphologic features of FHTCL without the histiocytic component seen in this case. It is not clear if long-term treatment for presumed Castleman disease with siltuximab and steroids led to alteration of the tumor microenvironment, supporting the histiocytic infiltrate.

In addition, this case shows the use of ancillary testing in diagnosis of a difficult T-cell lymphoma. The identification of the *IDH2* mutation using immunohistochemistry, as well as support for clonality with lack of TRBC1 in the atypical T-cells, show the utility of immunohistochemical stains in lymphoma diagnosis. This case of FHTCL shows characteristic molecular and immunophenotypic findings with an unusual morphologic pattern with a histiocytic infiltrate.

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-156

Peripheral T-Cell Lymphoma (NOS), lymphoepithelioid variant.

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Case Description

63-year-old man. PET-CT showed left axillary lymph node mass (192x50x95mm) SUVmax 42.8; right axillary two hypermetabolic lymph nodes, right paratracheal and subcarinal and paracardiac hypermetabolic lymph nodes. Liver parenchyma with multiple hypermetabolic foci occupying the entire parenchyma SUVmax 31. Lymph node conglomerate at the level of the hepatic hilum measuring 47 mm SUVmax 40. Multiple lymph nodes in the retroperitoneum up to the iliac bifurcation. Multiple hypermetabolic foci throughout the skeleton (rib cage, sternum, scapulae, spine, diaphysis of long bones, pelvis). Partial resection of axillary lymph mass was performed.

Biopsy Fixation Details

10% buffered formalin fixed and paraffin-embedded.

Frozen Tissue Available

Not-available.

Details of Microscopic Findings

The histological sections examined correspond to a lymph node showing altered architecture, due to a polymorphic lymphoid population with a predominance of medium to large-sized cells, some of which have a prominent nucleolus and poorly defined cytoplasm, and abundant accompanying epithelioid histiocytes. Multiple mitotic figures are observed.

Immunophenotype

The neoplastic cells are T lymphocytes expressing CD2, CD3, CD5, and CD8, with slight loss of CD7 and almost complete loss of CD4. Cytotoxic granules, TIA-1, and Granzyme B are positive in the neoplastic T cells. PD1 and ICOS (CD278) expression is preserved. Histiocytes are positive for CD68. Focal positivity of the dendritic network for CD23 and loss of CD21. Heterogeneous focal positivity in some accompanying B lymphocytes for CD79a, PAX5, and bcl-6 is observed. Isolated cells positive for CD30 and scattered cells positive for MUM. Negative expression is found for CD20, CD19, GATA 3, CD10, bcl-2 and c-myc. Ki-67 proliferative index: 45%.

In situ hybridization for the Epstein Barr virus (EBER probe) is negative.

Cytogenetics

Not-done.

Molecular Studies

PCR: Monoclonal band TCR-beta gene rearrangements of 249 bp, and biclonal band in Dbeta 2 region of 185 and 188 bp, were identified using BIOMED-2 protocol.

The NGS gene sequencing study (lymphoma panel) has not shown any contributing molecular alterations in either the current sample, with Ion AmpliSeq Liverpool Lymphoid Network Panel v2.

Proposed Diagnosis

Peripheral T-Cell Lymphoma (NOS), lymphoepithelioid variant.

Interesting Feature(s)

The presence of abundant epithelioid histiocytes raises the differential diagnosis with T-cell/histiocyte-rich large B-cell lymphoma and epithelioid cell-rich TFHL.

The presence of abundant accompanying epithelioid histiocytes and the cytotoxic profile (CD8 positive) are characteristic of the lymphoepithelioid variant (Lennert lymphoma), which is associated with a better prognosis.

Panel Diagnosis: nTFHL/TFHL with abnormal CD8+ cytotoxic T-cell population

Rhyme or reason: CD8+ Histiocyte-rich T-cell lymphoma with AITL-like genetics and a hint of POEMS

Dr. Brendan M. Barton¹, Dr. Philippe Armand², Dr. Elizabeth A. Morgan¹, Dr. Sam Sadigh¹

¹ Mass General Brigham, Pathology, Boston, USA; ² Dana Farber Cancer Institute, Medical Oncology, Boston, USA

Case Description

A 54-year-old man with malaise, dyspnea, abdominal pain, lower leg edema, and neuropathy had anemia, hypercalcemia, acute kidney injury, elevated κ/λ , and IgA κ M-spike. Imaging showed splenomegaly (25 cm), hepatomegaly and diffuse lymphadenopathy (up to 3.6 cm). A bone marrow biopsy with hypercellular marrow contained 25% κ -restricted plasma cells aberrantly expressing CD56, with scattered interstitial lymphoid aggregates, mostly CD3+ T cells. An outside lymph node biopsy was reportedly negative for lymphoma. Work-up for POEMS syndrome met insufficient criteria and Dara-CyBorD therapy for myeloma was initiated. Hospitalization for persistent COVID pneumonia with increasing lymphadenopathy prompted inguinal lymph node excision and repeat bone marrow biopsy.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded

Frozen Tissue Available

Yes

Details of Microscopic Findings

Excision demonstrates an enlarged lymph node diffusely effaced by an atypical lymphohistiocytic infiltrate of small- to medium-sized lymphocytes with oval to irregular nuclei, condensed chromatin, variably conspicuous small nucleoli, and scant amounts of cytoplasm. Numerous histiocytes with round ovoid nuclei, delicate chromatin, and moderate eosinophilic cytoplasm are present. Many intermixed eosinophils are present. No definitive Reed-Sternberg cells are seen. Background vascularity is increased. Frank necrosis is absent. Stains for microorganism were negative (AFB, MSS, FITE, Gram, mycobacterium). Bone marrow biopsy findings showed a similar lymphohistiocytic infiltrate.

Immunophenotype

CD3+ CD2+ CD5+/weak CD7weak CD8+ TCR-BF1+ PD1+(subset); ALK1- CD30- BCL6- CD10- CXCL13- cells varying in size. Numerous CD68+ CD163+ histiocytes are S100- CD1a- and langerin-. Flow cytometry demonstrates an inverted CD4:CD8 ratio of 0.2. The Ki-67 proliferation index is 30-40%. No CD138+ plasma cells, or CD21+ or CD23+ follicular dendritic cells are seen. EBER ISH and HHV8 are negative. ERG highlights increased background vascularity. Bone marrow biopsy findings demonstrate a similar immunophenotype.

Cytogenetics

48-49,XY,+X,add(1)(q25),add(2)(q25),add(2)(q25)[3],add(3)(p25), +mar[cp9]/46,XY[1]

Molecular Studies

TCR clonal pattern (Vgamma1-8 207bp primer) with NGS showing mutations in *KRAS* (p.A146V), *RHOA* (p.G17V), *TET2* (two deletions), *BCL6*, *CTNNB1*, and *NOTCH3*, and CNVs in 2q (gain; *CASP8*, *SF3B1*, *CTLA4*) and 9q (loss; *CDKN2A*, *CDKN2B*, *MTAP*).

Proposed Diagnosis

Peripheral T-cell lymphoma, not otherwise specified

Interesting Feature(s)

The case demonstrates a clinical presentation suspicious for POEMS syndrome, later diagnosed as multiple myeloma. Subsequent lymph node excision revealed a T-cell lymphoma with unique features:

- Prominent histiocyte-rich component with "Lennert-like" features
- NGS profile reminiscent of angioimmunoblastic T-cell lymphoma (*TET2*, *RHOA*) but CD8-positive tumor cells lack substantial TFH markers with absent FDC meshworks and negative EBV

-AITL with concurrent plasma cell proliferations, neoplasms or even POEMS syndrome is previously described, and CD4+ TFH tumor cells are thought to promote reactive or even clonal B-cell proliferations; however, a link with CD8+ cells is not established, though a physiologic counterpart follicular CD8+ T cell expressing PD-1, BCL-6, and CD40L – not seen here – could theoretically promote B-cell differentiation (PMID: 41357603, 25663904, 27501245, 27487330).

Overall, this unusual case challenges the diagnostician to integrate findings of myeloma, histiocyte-rich clonal T cells, and some clinical features of POEMS syndrome, which we find may be best characterized as two distinct malignant processes.

Panel Diagnosis: nTFHL /TFHL-NOS with granulomata

EA4HP26-LYWS-161

T-cell lymphoma with prominent histiocytes and angioimmunoblastic features

Dr. Brendan M. Barton¹, Dr. Natalie Rizzo², Dr. Elizabeth A. Morgan¹

¹ Mass General Brigham, Pathology, Boston, USA; ² MetroWest Medical Center, Pathology, Framingham, USA

Case Description

A 73-year-old female with ulcerative colitis presented with fatigue, dyspnea, cervical lymphadenopathy, and diffuse, pruritic rash. CBC revealed 11% atypical lymphocytes, including plasmacytoid forms. Neck CT showed cervical, mediastinal, and axillary lymphadenopathy up to 3.2 cm. SPEP found polyclonal hypergammaglobulinemia. A cervical node was excised.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded

Frozen Tissue Available

No

Details of Microscopic Findings

The sections show focally encapsulated lymphoid tissue with a diffuse, atypical infiltrate of predominantly small- to intermediate-sized lymphocytes with irregular nuclei, coarse chromatin, variably conspicuous nucleoli, and minimal pale cytoplasm. Admixed are scattered larger-sized atypical cells with irregular nuclear contours, vesicular chromatin, prominent nucleoli, and scant cytoplasm. A prominent histiocytic infiltrate is present, with diffuse clusters and aggregates of histiocytes. There is a background of numerous clusters of plasma cells and scattered eosinophils. Scattered mitotic figures are noted. Frank necrosis is not seen. Prominent background vascularity present.

Immunophenotype

Small- and intermediate-sized and scattered larger CD3+/weak cells with a CD4:CD8 ratio of approximately 1:1 and subset positive for PD-1, CXCL-13, CD10 (also by flow cytometry, FC), and BCL-6 and skewed towards TRBC1-negative. A subset of CD4+ cells by FC show slightly dim CD3 expression. Scattered larger forms are positive for CD45, CD20, PAX5 and CD30 and appear positive for EBER ISH. Multifocal, expanded CD21+ follicular dendritic cell meshworks present. CD138+ plasma cells aggregates polytypic by ISH for kappa and lambda immunoglobulin are present. CD68+ PU.1+ highlights histiocyte clusters throughout. HHV8 is negative. CD15 highlights scattered granulocytes and rare large cells.

Cytogenetics

47,XX,+3[cp5]/46,XX[15]

Molecular Studies

TCR testing detected clonal rearrangements of Vgamma1-8 and Vgamma9. IgH testing showed a polyclonal pattern. NGS studies on the lymph node were not performed. Staging bone marrow suspicious for lymphoma involvement

demonstrated the same Vgamma1-8 rearrangement and a *DNMT3A* I471Lfs*180 variant (1.2% VAF); no *TET2* or *IDH2* mutation; *RHOA* not tested.

Proposed Diagnosis

Follicular helper T-cell lymphoma, angioimmunoblastic type (TFHL-AI)

Interesting Feature(s)

The case demonstrates a patient presenting with a diffuse pruritic rash, lymphadenopathy and circulating lymphoplasmacytoid cells.

-Morphologic features including numerous histiocytes intermixed with many small lymphocytes evokes an impression classic for a Lennert-type peripheral T-cell lymphoma (PTCL-NOS)

-Additional scattered eosinophils and scattered large atypical lymphoid cells are reminiscent of mixed cellularity subtype of classic Hodgkin lymphoma, though diagnostic Reed-Sternberg cells are not identified.

-CD4+ clonal T cells, increased vascularity, abnormal follicular dendritic cell meshworks, subset expression of TFH markers supports classification as follicular helper T-cell lymphoma, angioimmunoblastic type (TFHL-AI); clinical features also supportive.

-Findings of expanded FDC meshworks, prominent HEVs, and polymorphic infiltrate as demonstrated in recent literature distinguish TFHL-AI with abundant histiocytes from Lennert-type PTCL-NOS, particularly in cases with TFH marker expression; however, as discussed in a prior SH-EAHP workshop, absent these findings, a differential of TFHL-NOS and PTCL-NOS may require integration of the number of TFH markers expressed, NGS, and clinical behavior for definitive diagnosis (PMID: 22175897, 27428734, 37500795).

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-164

A Case of Limited Stage T-Cell Lymphoma with T Follicular Helper Cell Phenotype

Dr. Paula Cortes Barrantes, Dr. Hariharan Hariharan Bharadwaj

Baystate Medical Center, Pathology, Springfield, USA

Case Description

A 90-year-old woman with multiple comorbidities, had a fall in February 2025, following which she noticed a left axillary mass. In July 2025, as part of a breast routine work up, a left axillary mass was noted. Ultrasound described the lesion as a lobular, solid, hypoechoic vascular mass measuring 3.8 x 2.6 x 2.2 cm concerning for malignancy, but not definitely a primary breast abnormality. The patient denied fevers, unintentional weight loss, headaches, vision changes or erythromelalgia. A review of systems was negative except for several years of night sweats. An axillary lymph node biopsy was performed. PET-CT showed no additional disease. The patient received palliative local radiotherapy with excellent response. Subsequent peripheral blood flow cytometry identified a small, atypical T-cell population, suggesting possible low-level persistent disease.

Biopsy Fixation Details

Two tissue cores submitted in formalin.

Frozen Tissue Available

Not submitted.

Details of Microscopic Findings

Histologic examination showed effacement of architecture with prominent perifollicular expansion and residual follicles. The infiltrate was polymorphous, composed of small- to medium-sized lymphocytes with scattered immunoblasts, plasma cells, histiocytes, and numerous eosinophils among prominent high endothelial venules.

Immunophenotype

Immunohistochemistry demonstrated a predominance of CD3-positive T cells co-expressing CD4, CD5, and BCL-2, with expression of PD-1 and ICOS, weak BCL6 positivity, and negativity for CXCL13. Scattered CD8-positive T cells were present. CD23 highlighted expanded follicular dendritic cell (FDC) meshworks.

Cytogenetics

Not performed.

Molecular Studies

Positive clonal T-cell receptor beta and gamma gene rearrangements.

Proposed Diagnosis

T cell lymphoma with a T Follicular Helper Cell phenotype.

Interesting Feature(s)

Indolent nodular TFH lymphomas have been associated with prolonged survival, responding to conservative management including localized radiotherapy, with rare reports of spontaneous remission. Indolent cases of angioimmunoblastic T-cell lymphoma (AITL) typically show histologic patterns 1 or 2. Our case demonstrated predominant interfollicular expansion with residual follicles, consistent with AITL pattern 2.

TFH lymphomas exemplify the critical role of the tumor microenvironment (TME) in pathogenesis. Neoplastic TFH cells comprise a minor fraction of the lesion⁶ and interact with surrounding T and B cells, FDCs, and Epstein–Barr virus (EBV) –infected B cells, particularly in early tumorigenesis. CXCL13 produced by TFH cells promotes B-cell expansion and plasmacytic differentiation, contributing to immune dysregulation. TFH cells and mast cells secrete vascular endothelial growth factor, leading to FDC expansion and proliferation of high endothelial venules. FDCs and macrophages produce pro-inflammatory cytokines, including interleukin-6, which support malignant T-cell proliferation, while increased interleukins 4, 5, and 13 contribute to eosinophil-rich infiltrates.

Alterations in the TME have diagnostic and prognostic implications. A prominent reactive component may obscure neoplastic cells, and EBV-positive B-cell blasts can mimic Hodgkin/Reed–Sternberg cells, complicating diagnosis. An immunosuppressive TME enriched in CD8+ tumor-infiltrating lymphocytes has been associated with poorer prognosis. Similar microenvironmental influences are observed in other peripheral T-cell lymphomas, including follicular and lymphoepithelioid variants and ALK-positive ALCL. Understanding TME-driven effects on the neoplastic clone may offer future therapeutic opportunities.

Panel Diagnosis: PTCL, suboptimal small sample, likely nTFHL/TFHL

EA4HP26-LYWS-179

Systemic/ Leukemic Involvement by ALK+ Anaplastic Large Cell Lymphoma with Associated Hemophagocytic Lymphohistiocytosis

Dr. Hannah Cutshall, Dr. Swathi Muni Reddy, Dr. Susan Harley, Dr. Jeanette Ramos

University of Arkansas for Medical Sciences, Pathology, Little Rock, USA

Case Description

A 45-year-old male presented to the Emergency Department with acute hypoxic respiratory failure. Further investigation revealed night sweats, intermittent fevers, and unintentional weight loss over several months.

On presentation, hemophagocytic lymphohistiocytosis (HLH) was suspected given his persistent fevers, splenomegaly, cytopenias, hyperferritinemia (18,045 ng/mL), hypertriglyceridemia (426 mg/dL), and diffuse lymphadenopathy. His IL-2 later returned markedly elevated at 434,460.7 pg/mL. A peripheral blood smear and bone marrow biopsy were obtained. The patient decompensated clinically. Based on preliminary bone marrow results, he was started on treatment with cytarabine and cladribine. He died approximately two weeks after admission, and an autopsy was performed.

Biopsy Fixation Details

AZF-fixed and paraffin-embedded

Frozen Tissue Available

None

Details of Microscopic Findings

Peripheral blood: Circulating abnormal intermediate to large mononuclear cells have irregular nuclear contours, dispersed chromatin, prominent nucleoli and scant to moderate basophilic cytoplasm. A subset have cytoplasmic vacuoles.

Bone Marrow Aspirate/Biopsy: A population of large, abnormal mononuclear cells (20-30%) are present, with an interstitial distribution, intermixed with the left-shifted trilineage hematopoietic cell population. Abnormal cells are also identified within sinusoids.

Increased histiocytes are also distributed within marrow elements and present in sinuses; a subset demonstrate hemophagocytosis. Histologic sections from autopsy revealed extensive involvement by ALK-positive anaplastic large cell lymphoma (ALCL) involving: all submitted lymph nodes (supraclavicular, axillary, inguinal, hilar, paraesophageal, peripancreatic, perihepatic and mesenteric). ALCL also involved the epicardium with perivascular involvement of the left anterior descending, left circumflex and right coronary arteries as well as the liver, spleen, left adrenal gland, prostate, appendix, thyroid, esophagus, bilateral lungs and kidneys, and leptomeninges.

Immunophenotype

Flow Cytometry of the peripheral blood showed an atypical CD4/CD56 positive population. Immunohistochemical staining of the bone marrow and lymph node showed the neoplastic cells were positive for CD30 and ALK.

Cytogenetics

44~45,X,-Y,+2,add(2)(p13),t(2;15)(p23;q22)[cp16]/46,XY[3]/ 46,XY,tr(1)(q10)[1]

Molecular Studies

FISH showed an *ALK* rearrangement which was shown to be inv(2)(p23q35) *AT1C::ALK* fusion by NGS.

Proposed Diagnosis

Widespread involvement by ALK-positive ALCL with associated HLH

Interesting Feature(s)

This was a difficult case given the leukemic presentation and lack of lineage-specific markers on initial flow cytometry. The expression of only CD4 and CD56 raised an initial differential diagnosis of acute myeloid leukemia (AML) with monocytic differentiation with aberrant loss of lineage-defining myeloid/monocytic markers or blastic plasmacytoid dendritic cell neoplasm (BPDCN). Further evaluation of the abnormal cells lacked expression of CD123. Immunohistochemical expression of CD30 and ALK-1 by the abnormal cells brought ALCL into the differential. However, ALK-positive AML has also been reported. The association with HLH/increased histiocytes that were in the sinusoids made interpretation of histiocytic markers difficult on the neoplastic cells. The diagnosis was clinched on the lymph node staining pattern at autopsy. FISH is positive for an *ALK* rearrangement with an uncommon rearrangement partner: *AT1C::ALK* fusion. This case displayed extensive multisystem involvement by ALCL, including involvement of the coronary arteries and the leptomeninges.

Panel Diagnosis: ALK+ ALCL in leukemic phase and with HLH

ALK-positive Anaplastic Large Cell Lymphoma, lymphohistiocytic pattern

Dr. Jhuma Nandi, Dr. Yi Sun

Rutgers Robert Wood Johnson Medical School, Pathology & Laboratory Medicine, New Brunswick, USA

Case Description

A 12-year-old male with a history of eosinophilic esophagitis, celiac disease, and asthma presented with right cervical lymphadenopathy. Laboratory studies were significant for mild anemia with hemoglobin of 11.6 g/dL, and mildly elevated LDH (255 U/L). Imaging revealed mediastinal, supraclavicular, and hilar lymphadenopathy. Excisional biopsy of a right cervical lymph node demonstrated effaced architecture by sheets of large atypical lymphoid cells with irregular nuclei and frequent hallmark cells. Immunophenotyping identified an abnormal T-cell population, co-expressing strong CD30 and ALK, consistent with ALK-positive anaplastic large cell lymphoma (ALCL), common pattern. The patient was treated per the ANHL12P1 Arm BV protocol. Six weeks after completion of therapy, he presented with relapse. Lymph node biopsy showed diffuse lymphohistiocytic infiltrate, composed predominantly of small to medium sized lymphocytes admixed with abundant histiocytes, consistent with ALCL, lymphohistiocytic pattern. The patient underwent allogeneic HSCT and now in remission (5 months post transplant).

Biopsy Fixation Details

Fixation was done in 10% neutral buffered formalin for at least 6 hours before processing.

Frozen Tissue Available

Frozen tissue is not available.

Details of Microscopic Findings

First biopsy: H&E stained sections show lymph node with effaced architecture by dense infiltration of large atypical lymphocytes with irregular nuclei and frequent hallmark cells.

Biopsy at relapse: lymph nodes show effaced architecture by diffuse lymphohistiocytic infiltrate, composed of mostly small to medium sized lymphocytes, and occasional large lymphocytes, with moderate to abundant eosinophilic cytoplasm, admixed in a background of numerous histiocytes, and scattered plasma cells.

Immunophenotype

Initial biopsy: strong CD30, CD2, CD7, ALK and negative for sCD3, CD4, CD8, CD56, CD5, B-cell markers.

biopsy at relapse: variable CD30, CD2, CD7, ALK, variable cytoplasmic CD3, while negative for CD4, CD8, sCD3, CD5.

Cytogenetics

At relapse: Karyotyping reveals 47,XY,t(2;5)(p23;q35),+7,del(20)(q11.2)[12]/46,XY[2]

abnormal male karyotype with a translocation between chromosomes 2 and 5, trisomy 7 and deletion of the long arm of chromosome 20.

Molecular Studies

FISH study is positive for ALK translocation.

Proposed Diagnosis

ALK-positive Anaplastic Large Cell Lymphoma, lymphohistiocytic pattern, at relapse

Interesting Feature(s)

ALK positive anaplastic large cell lymphoma (ALCL) is rare and mature T-cell lymphoma, typically occur in children and young adults with a male predominance, accounting for 10–15% childhood and ~ 3% of adult non-Hodgkin lymphomas. ALCL shows morphologic heterogeneity, including common, small cell, lymphohistiocytic, Hodgkin-like, composite patterns. The lymphohistiocytic pattern (~10% of ALCL) is characterized by abundant reactive histiocytes and smaller lymphocytes that may obscure the neoplastic cells, making diagnosis challenging. Also, presence of lymphohistiocytic component indicates a high risk of treatment failure. Our case presented with common pattern but relapsed with lymphohistiocytic pattern.

EA4HP26-LYWS-190

Boundaries Between Reactive and Neoplastic: A Diagnostic Challenge in Nodal T-Follicular Helper Cell Lymphoma

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Rede D'OR São Luiz, Pathology, São Paulo, Brazil

Case Description

A 56-year-old female patient presented with one month of persistent fever and cervical lymphadenopathy. Imaging studies confirmed lymph node enlargement. Serology tests for HIV, EBV, CMV, herpes and hepatitis were negative. An excisional biopsy of a posterior cervical lymph node measuring 1.4 × 1.0 cm was obtained. The initial histopathological diagnosis was reactive lymphoid hyperplasia with a mixed follicular and paracortical pattern.

The patient was treated with corticosteroids, resulting in regression of lymphadenopathy and systemic symptoms. However, following treatment discontinuation, she experienced progressive lymph node enlargement accompanied by persistent fever. Given the clinical relapse, a histopathological slide review was requested.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The lymph node exhibited partial preservation of its architecture. Lymphoid follicles were moderately enlarged, showing reactive germinal centers with focal attenuation of the mantle zones.

The paracortical region was expanded and composed of a polymorphic lymphoid population, predominantly small- to intermediate-sized lymphocytes with mild cytologic atypia, characterized by irregular nuclear contours and moderate clear cytoplasm. These cells were distributed around lymphoid follicles and within the paracortex, occasionally showing a perivascular arrangement surrounding high endothelial venules. Scattered large pleomorphic cells were also identified, along with histiocytes, neutrophils, and eosinophils. Focal vascular proliferation was present.

Immunophenotype

The intermediate-sized atypical lymphoid cells were positive for CD3, CD5, CD4, and partial CD30, as well as T-follicular helper (TFH) cell markers, including CD10, focal BCL-6, and PD-1. A partial loss of CD7 expression was observed.

Immunohistochemistry for TRBC1/CD3 demonstrated a monotypic pattern with negative TRBC1 expression in the areas of interest.

The follicular dendritic cell meshwork was focally expanded. EBER in situ hybridization was positive in paracortical B immunoblasts.

Cytogenetics

Not available.

Molecular Studies

Not available.

Proposed Diagnosis

Nodal T-follicular helper (TFH) cell lymphoma, angioimmunoblastic type, corresponding to patterns 1 and focal pattern 2.

Interesting Feature(s)

This case represents a diagnostic challenge, as it involves a lymphoid neoplasm with partial architectural preservation, a rich inflammatory microenvironment, and subtle morphologic abnormalities, closely mimicking reactive conditions. The use of an extended immunohistochemical panel was crucial, particularly the identification of a TFH phenotype and demonstration of aggregates of monotypic T-cells through TRBC1/CD3 immunohistochemistry, which suggests a clonal T-cell population around follicles and within the paracortical region. The purpose of reporting this case is to emphasize the importance of maintaining a high index of suspicion for this rare and often underrecognized entity, especially in cases initially interpreted as reactive lymphoid hyperplasia.

Panel Diagnosis: nTFHL/TFHL-AI, pattern 1

EA4HP26-LYWS-193

Nodal T follicular helper cell lymphoma NOS with Lennert-like Granulomas Masquerading as Lennert Lymphoma: A Prototypic Pitfall in Epithelioid Histiocyte-Rich (Granulomatous) T-cell lymphoma

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Case Description

A 63-year-old female presented with an enlarging neck mass and a prior history of atypical CD4+ lymphocytic infiltrate in the left breast skin rash. PET-CT: FDG-avid multi-station lymphadenopathy (neck, lungs, axilla, inguinal, pelvic; up to 2.4 cm; SUV 3.7–6; Deauville 5). Despite advanced-stage disease, the clinical course was indolent. The patient was treated with CHOP (ongoing, cycle 3/6; indolent course, well tolerated).

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

Hypopharyngeal excisional biopsy showed benign non-keratinized squamous mucosa with submucosal non-necrotizing granulomas and polymorphous infiltrate of atypical small lymphocytes, polytypic plasma cells, and scattered immunoblasts.

Immunophenotype

Flow cytometry: Aberrant CD3 (dim)+CD4+CD7-CD2+CD5+TCRαβ (dim)+ T-cells (57% lymphocytes)
IHCs: Aberrant CD3+CD4+ T-cells express GATA3 (partial), ICOS (strong diffuse), PD1(partial), CXCL13/CD10/BCL6(subset), CD2/CD5/BCL2/CD30(var)/CD7(subset); CD21/CD23 showed disrupted follicular dendritic cell meshworks with focal extrafollicular expansion. IHC for TBX21, CXCR3, and CCR4 pending.

Cytogenetics

CMA: del(5q22.2–q23.1) (~40%), cnLOH 7q35–qter (~100%).

Molecular Studies

NGS (275-gene panel): Biallelic TET2 LOF (p.Phe387Hisfs2 VAF 17%; p.Gln1523 VAF 16%).
Clonal TCRγ gene rearrangement: Biallelic (Vγ10-Jγ1/2 35%; Vγ2-Jγ1/2 26%)

Proposed Diagnosis

Nodal T-follicular Helper Cell Lymphoma NOS, involving Waldeyer's ring, with Lennert-like Granulomatous Reaction

Interesting Feature(s)

This case highlights a diagnostic pitfall in granulomatous T-cell lymphomas, where Lennert-like morphology obscures an underlying TFH-derived neoplasm that can only be resolved by integrated immunophenotypic and genomic profiling. A diffuse non-necrotizing Lennert-like granulomatous background initially suggested Lennert lymphoma (lymphoepithelioid PTCL-NOS variant) given CD4 predominance, despite lacking a cytotoxic phenotype. The CD4/CD8 expression pattern in LL remains controversial—while Hartmann et al. (2011) reported a non-activated cytotoxic profile often missing CD8, Etebari et al. (2019) described CD4+ helper predominance. In our case, the absence of cytotoxic markers prompted a full TFH evaluation, revealing a strong TFH phenotype. Kurita et al. 2016 demonstrated TFH marker expression in many Lennert-like PTCLs, suggesting a biologic overlap with nTFH lymphomas. Erzar et al. (2025) showed that biallelic/multiple TET2 mutations—almost exclusive to nTFHL—served as a molecular anchor for reclassifying many PTCL-NOS cases into the TFH category. Our case harbored biallelic TET2 loss-of-function variants, supporting nTFHL, despite its Lennert-like morphology. Notably, the low complexity CMA (5q22.2–q23.1 deletion, 7q cnLOH) aligned with the PTCL–TBX21–like molecular cluster rather than high-complexity PTCL–GATA3. Non-cytotoxic Lennert pattern in TBX21 cases fares better than cytotoxic Lennert pattern. This genomic configuration corresponds to the favorable “C1” cluster described by Suehara et al. (2025), characterized by epigenetic regulator mutations (including biallelic TET2) without chromosome 5 amplification, IDH2 mutations, or high aneuploidy—consistent with the patient’s indolent stage IV disease and favorable response to CHOP.

This case demonstrates that Lennert-like granulomatous T-cell lymphomas should not be classified based on morphology and immunohistochemistry alone, underscoring the need for integrated TFH immunophenotyping, next-generation sequencing, and copy number analysis for accurate classification and clinical management of granulomatous PTCL.

Panel Diagnosis: nTFHL /TFHL-NOS with granulomata

EA4HP26-LYWS-197

Unusual immunophenotypic and molecular features of nodal T-cell lymphoma with prominent histiocytes, designated as anaplastic large cell lymphoma as consensus diagnosis at multidisciplinary meeting

Dr. Olena Dotsenko, Prof. John Schofield

Maidstone and Tunbridge West NHS Trust, Cellular pathology, Maidstone, UK

Case Description

62-year-old man presented with generalised lymphadenopathy and B symptoms. The first biopsy originated from axilla and was provisionally reported by breast pathology team as pleomorphic lobular carcinoma. Small core of tissue was exhausted for ancillary studies and an excisional biopsy of the right axillary lymph node followed.

An excisional biopsy revealed seminecrotic enlarged lymph node, populated by sheets of large cells with variable morphology on immunohistochemistry, expressing several T-cell markers, cytotoxic markers, showing strong, but patchy CD30 expression and some unconventional immunophenotypic features and molecular features.

Diagnosis of PTCL, NOS was suggested initially, but agreed as ALK-negative anaplastic large cell lymphoma at multidisciplinary meeting for patient management purposes.

Biopsy Fixation Details

10% Neutral Buffered formalin

Frozen Tissue Available

Not done

Details of Microscopic Findings

The enlarged lymph node showed variably thickened capsule, residual tiny background follicles at the periphery and replacement of normal architecture by sheets of large atypical lymphocytes with variable morphology, including multinucleated cells, immunoblasts, Reed-Sternberg like cells and hallmark like cells, associated with areas of impending necrosis, sheets of epithelioid histiocytes, numerous eosinophiles and small lymphocytes. Plasma cells appeared in small numbers. Marked mitotic activity and apoptosis were associated with atypical lymphocytes, but starry sky pattern was not seen.

Immunophenotype

Positive: CD43, CD4, CD2, CD3, myeloperoxidase (patchy), CD68 (heterogenous), CD30 (patchy strong diffuse), GATA3/MUM1/BCL6 (weak), BLIMP1, BCL2, TIA1, granzyme B, perforin and focal ICOS. Negative for CD138, MUM1, CD10, cytokeratins, SOX10, CD20, CD79a, PAX5, OCT2, BOB1, HHV 8, CD23, ALK1, CD138, EMA, CD34, CD117, S100, CD56, CD15, mostly negative for CD5 and CD7 and showed some heterogeneity in staining for CD45 (predominantly negative), PD1 and CXCL13.

There were no associated FDCs on CD21 and CD23 (but residual present in the background follicles).

EBV LMP 1 and EBER highlighted small number of larger cells with B-cell immunophenotype.

Ki-67 proliferation index was around 75-95%.

Cytogenetics

Not done

Molecular Studies

No *ALK*, *DUSP22* and *TP63* rearrangements were detected by FISH.

IGH C and IGK B clonal gene rearrangements in a polyclonal background were detected. TCR B C gene rearrangement clonal gene rearrangement in polyclonal background was detected. TCRG, TCR B, TCR B gene rearrangement testing failed due to lack of amplification in major targets.

Repeated clonality testing and lymphoma gene panel results are pending.

Proposed Diagnosis

ALK-negative anaplastic large cell lymphoma. Differential diagnosis includes peripheral T-cell lymphoma, NOS. Adult T-cell leukaemia/lymphoma, T/myeloid MPAL, ETP-ALL, myeloid cell and histiocytic/transdifferentiated neoplasms have been considered, but based on morphology and immunophenotype, were regarded as less likely entities.

Interesting Feature(s)

Some unusual morphological features included focal prominent histiocytosis, associated with neoplastic cells, patchy neoplastic cells' expression myeloperoxidase, CD68 and BLIMP1, considered as aberrant/non-specific, focal patchy EBV LMP 1 and EBER expression by larger cells with B-cell immunophenotype (OCT2, BOB1, CD20 and PAX5 positive). Unusual molecular features included detected IGH and IGK gene clonal rearrangements (in polyclonal background) in addition to TCRB C clonal rearrangement (in polyclonal background).

Panel Diagnosis: Mixed phenotype (myeloid/T) acute leukemia

T-cell lymphoma with lymphoepithelioid (Lennert-like) morphology and TFH immunophenotype

Dr. Olga Kouroukli, Dr. Christos Masaoutis, Dr. Georgios Kanellis, PhD/MD Evdoxia Pouliou, M.Sc./M.A. Lamprini Vlachogianni, PhD/MD Elissavet Oikonomaki, Dr. Leonidas Marinos, Dr. Asimina Papanikolaou

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Case Description

We report the case of the 60-year old female patient. During the workup for pancytopenia, a bone marrow biopsy revealed a marked interstitial T-cell infiltration (~35%), raising suspicion for a T-cell lymphoma. A biopsy of a 1.2 cm cervical lymph node was subsequently performed. Histologic examination showed effacement of the lymph node architecture by a polymorphic infiltrate, predominantly composed of atypical T cells and prominent epithelioid histiocytes. The T-cell population expressed T follicular helper (TFH) markers, supporting a diagnosis of a nodal TFH lymphoma according to the WHO 2022 classification.

Biopsy Fixation Details

The biopsy specimen was fixed in 10% neutral buffered formalin prior to processing.

Frozen Tissue Available

No frozen tissue is available.

Details of Microscopic Findings

The lymph node showed architectural effacement with absent follicles and a diffuse polymorphic infiltrate. Clusters of epithelioid histiocytes, including occasional multinucleated giant cells, were distributed throughout the lymph node and intermingled with a diffuse population of atypical T cells. The T cells were small to medium-sized with slightly irregular nuclear contours and coarsely distributed chromatin. Rare, larger immunoblastic-like cells were present, along with a moderate number of scattered eosinophils and plasma cells. There was no evidence of prominent vascular proliferation.

Immunophenotype

The atypical T cells were positive for CD3, CD5, CD4 and to a lesser extent for CD8. Expression of TFH markers was observed, namely frequent PD-1, CD10 and ICOS positivity and rare CXCL13 expression.

The cytotoxic marker TIA-1 was expressed, with focal granzyme B positivity. CD30 stained partially the neoplastic cells, as well as immunoblastic cells. CD15 expression was restricted to granulocytes.

CD20 stained a small number of B cells, mainly forming small aggregates and a thin subcapsular zone.

Rare follicular dendritic cell remnants were identified by CD21 and CD23 staining.

Cytogenetics

No cytogenetic studies are available.

Molecular Studies

BIOMED-2 PCR clonality analysis showed monoclonal TRG (VJa) rearrangements.

NGS analysis (Euroclonality-NDC panel) identified three TET2 variants (c.4151A>G VAF=18.6%; c.4854C>A VAF=6%, c.4100C>T VAF=4.4%) and monoclonal TR rearrangements (TRA, TRB, TRG). No mutations in RHOA or IDH2 genes were detected.

Proposed Diagnosis

The case was diagnosed as nodal TFH lymphoma, not otherwise specified (NOS) due to the TFH immunophenotype and the absence of features of TFH, angioimmunoblastic or follicular type.

Interesting Feature(s)

Expression of TFH markers is infrequently observed in T-cell lymphomas with lymphoepithelioid (Lennert-like) morphology and has been identified as a poor prognostic factor. According to the 2022 WHO classification, such cases should be classified as nodal TFH lymphomas rather than peripheral T-cell lymphomas, NOS.

In the present case, positivity for multiple TFH markers was observed, along with CD10 expression, a finding that has been only rarely reported in Lennert-like lymphomas. CD10 expression increased specificity for a diagnosis of TFH lymphoma. The presence of TET2 mutations, a recurrent –though not specific– finding in TFH lymphomas, is in keeping with this diagnosis.

Panel Diagnosis: nTFHL /TFHL-NOS with granulomata

EA4HP26-LYWS-216

Evolution of Cytotoxic Peripheral T-cell Lymphoma with Lennert Pattern

Dr. Parastou Tizro, Dr. Winston Lee, Prof. Lorinda Soma, Prof. Joo Song

City of Hope Medical Center, Pathology, Duarte, USA

Case Description

A 39-year-old man presented with a progressively enlarging submental mass. Biopsy demonstrated peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), with a cytotoxic immunophenotype and Lennert-type morphology; clinically stage IVA disease. The patient was treated with 6 cycles of CHOEP chemotherapy and high-dose methotrexate, followed by autologous HSCT. He experienced multiple biopsy-confirmed relapses. Notably, the relapsed disease demonstrated a gradual phenotypic shift over time from a CD8-dominant cytotoxic profile to predominance of CD4-positive T cells, while Lennert-type features persisted and EBER-ISH remained negative. He was subsequently treated with azacitidine in combination with romidepsin, achieving an initial partial response followed by disease progression. Biopsy of an FDG-avid cervical lymph node revealed recurrent PTCL-NOS with an EBV-positive large B-cell lymphoproliferative disorder (B-cell LPD). A subsequent biopsy from a different anatomic site two months later showed a mixture of CD4- and CD8-positive atypical T cells and a return to EBV-negative status.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

- **Initial biopsy:** Effaced lymph node architecture by a diffuse infiltrate of atypical small to medium-sized lymphoid cells admixed with numerous clusters of epithelioid histiocytes
- **At relapse with B-cell LPD:** Effaced lymph node architecture by a pleomorphic infiltrate composed of atypical lymphoid cells, mostly medium-sized with irregular nuclear contours and coarse chromatin, admixed with large clusters of epithelioid histiocytes. Some large, atypical cells reminiscent of Hodgkin/RS-like cells. These large cells formed conspicuous clusters and focal confluent sheets

Immunophenotype

- **Initial biopsy**
- Positive: CD2, CD3, CD5, CD7 (decreased), CD8, TIA-1, PD-1 (subset), Ki-67 (~40%)
- Negative: CD4, CD15, CD20, CD56, ALK, BCL6, granzyme B, perforin, PAX5
- **At relapse**
- Positive: CD3, CD4 (predominantly), CD5 (decreased), CD7 (decreased)
- Negative: CD8, PD-1, TIA1, perforin, granzyme, ALK
- **Large cells:** Positive for CD30, CD15, CD20, PAX5, OCT2, CD79a, MUM1, EBER-ISH

Cytogenetics

N/A

Molecular Studies

Initial biopsy:

- *CUX1* (p.S1389Rfs*58), *TET2* (p.N275Ifs*18)

Presumed Relapses (post-HSCT):

- **6 months (CD8-dominant):**
- TCR γ (155 bp) and TCR β (262 bp) gene rearrangements
- *TET2* (p.N275Ifs*18)
- **14 months (CD4>CD8):** TCR γ (187 bp, 199 bp) and TCR β (262 bp) rearrangements
- **16 months (CD4+ T-cell lymphoma & EBV+ B-cell LPD):**
- *NF1* (p.I679fs*21), subclonal
- IGK rearrangement detected
- TCR rearrangement pending
- **21 months (CD8>CD4):** NGS in process.

Proposed Diagnosis

- Peripheral T-cell lymphoma, NOS, Lennert type
- Large B-cell lymphoproliferative disorder, EBV-positive

Interesting Feature(s)

- Phenotypic plasticity of the T-cell lymphoma; biologic heterogeneity
- Co-occurrence of *TET2* and *CUX1* mutations, consistent with an epigenetically primed, genomically unstable lymphoma
- *NF1* loss-of-function mutation (consistent with *RAS/MAPK* pathway activation) raising possibility of clonal evolution and/or clonal selection
- Secondary EBV+ B-cell LPD; immune dysregulation /microenvironmental changes
- *TET2* mutation, raising the possibility of ancestral clonal hematopoiesis

Follow-up: He received CD70-targeted CAR-T therapy with transient response, followed by gemcitabine+ oxaliplatin (GemOx) and allogeneic HSCT, resulting in sustained remission.

Panel Diagnosis: NO POWERPOINT -CASE NOT REVIEWED

EA4HP26-LYWS-217

Nodal TFH-cell lymphoma NOS masked by epithelioid cells and apoptotic necrosis

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Case Description

78 year-old female

Cervical bilateral polyadenopathies (2A right and left; 3 and 4 left) rapidly growing in May 2025, stable until December 2025.

No fever, sweats or weight loss

PET TDM :Intense hypermetabolism of bilateral cervical adenopathies and right tonsil; no other fixations

CBC and CRP normal

Left cervical lymph node excision

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

thick lymph node capsula

destruction of normal lymph node architecture

Ill defined areas of necrosis with apoptotic bodies

lymphoepithelioid sheets with vascular hyperplasia, rare plasma cells and few eosinophils

Ziehl and GWS negative

Immunophenotype

anti-CD20 underlined primary follicles, prominent small B-cell expansion with no B-cell immunoblastic hyperplasia

Majority of cells are CD3+ CD4+ CD7+ T-cells mainly small with few middle-size T-cells

Presence of small nests of PD1+ CXCL13+ CD10+ T-cells

Hyperplasia of medium large CD8 T cells, granzyme B+

Very focal minimal expansion of CD21+ FDC

EBER negative

Cytogenetics

No

Molecular Studies

Clonal rearrangement of TCR gamma gene and no rearrangement of IgH and Kappa genes

NGS : RhoA G17V mutation (VAF 6%) , TET2pA147fs (VAF8%)

Proposed Diagnosis

Nodal TFH-cell lymphoma NOS

Interesting Feature(s)

- Lymphoepithelioid pattern, thick capsula and apoptotic necrosis mimicking atypical lymphadenitis or histiocytosis and masking small aggregates of small to medium size TFH cells
- Indolent clinical presentation
- Importance of molecular tests and particularly NGS to confirm the diagnosis

Panel Diagnosis: nTFHL /TFHL-NOS with granulomata

EA4HP26-LYWS-225

T/NK-cell lymphoma with EBV related hemophagocytosis and with a bone marrow manifestation

Dr. Anna Kwiecinska, Dr. Leonie Saft, Prof. George Rassidakis

Karolinska University Hospital Solna, Solna, Sweden

Case Description

A 68 – year- old man admitted to a hospital with hyperinflammation, HLH and pancytopenia 1,5 month after heart surgery due to biological aortic valve replacement and aortic graft. CT scan showed no lymphadenopathy. Spleen

was enlarged 14 cm. Lab findings showed EBV 52 000 copies/ml in blood. The patient was treated for EBV infection. HLH and cytostatics but passed away 3 months later.

Biopsy Fixation Details

Formalin-fixed and paraffin-embedded bone marrow trephines (buffered 4% formalin).

Frozen Tissue Available

not available

Details of Microscopic Findings

The bone marrow biopsy and aspirate showed infiltration of atypical T-cells with immunophenotype: CD56+, CD7+, CD3 (weak +), CD2 (weak +) CD4-, CD8-, granzyme B+, GATA3 weak+, CD10-, PD-1-, bcl6-, CXCL13-, TBX21-, ALK1-. CD30 stained 2-5% positive T-cells. Double staining CD3/EBER ISH showed CD3+/EBV+double positive atypical T-cells. Staining for p53 was strongly positive indicating TP53 mutation. Prominent hemophagocytosis was observed.

Immunophenotype

Flow cytometry showed 3,7% cells with immunophenotype: CD56+/cytCD3+/mCD3-/CD5-/CD2+/CD7+/CD4-/CD8-/TCR Cb 1-/CD10-/CD57-

Immunohistochemistry: CD56+, CD7+, CD3 (weak +), CD2 (weak +) CD4-, CD8-, granzyme B+, GATA3 weak+, CD10-, PD-1-, bcl6-, CXCL13-, TBX21-, ALK1-, EBV+, CD30 subpopulation+ (2-5%)

Cytogenetics

not available

Molecular Studies

NGS analysis of bone marrow showed pathogenic TET2 mutation (VAF 4%) and p53 mutation (VAF 8%)

Proposed Diagnosis

T/NK-cell lymphoma with EBV related hemophagocytosis with sole bone marrow manifestation

Interesting Feature(s)

- 1) bone marrow manifestation, no lymphadenopathy. Slight splenic enlargement
- 2) rapid clinical course
- 3) association with EBV and HLH

Panel Diagnosis: Aggressive NK leukemia with HLH

EA4HP26-LYWS-253

Lymphoepithelioid lymphoma (Lennert lymphoma) with unusual phenotype

Dr. Haipeng Shao

Moffitt Cancer Center, Department of Pathology, Tampa, Germany

Case Description

The patient was a 65 year-old female who first noted a diffuse, pruritic and raised rash 7 years ago. She was treated with doxycycline, gabapentin, niacin, TAC, prednisone taper with initial relief, but the rash recurred upon complete of treatment. PET/CT scan showed FDG avid lymph nodes in the neck, left axilla, and left para-aortic retroperitoneal region. A left axillary lymph node biopsy was performed. After the diagnosis was confirmed, the patient was treated with CHOP chemotherapy. Subsequent PET scan was concerning for progressive spleen lesions. The therapy was changed to romedepsin and onureg with mixed response.

Biopsy Fixation Details

10% formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

The lymph node architecture is effaced by sheets of lymphohistiocytic infiltrate with numerous epithelioid histiocytes admixed with predominant small mature lymphoid cells and few scattered large lymphoid cells.

Immunophenotype

By immunohistochemical staining, the atypical lymphoid cells are positive for CD2, CD3 (weak and cytoplasmic), CD20 (weak), OCT2 (weak), TIA1, granzyme B, and negative for CD5, CD7, CD4, CD8, CD30, CD10, CXCL13, CD15, ALK and CD56. CD21 shows the residual follicular dendritic meshworks. EBER-ISH is negative.

Corresponding flow cytometry shows an abnormal population of T-cells with expression of CD2, and negative for surface CD3, CD4, CD8, CD5, CD7, CD30, TCR ab and TCR gd.

Cytogenetics

N/A

Molecular Studies

PCR study shows clonal TCR beta and TCR gamma gene rearrangements.

Proposed Diagnosis

Lymphoepithelioid lymphoma (Lennert lymphoma)

Interesting Feature(s)

The case shows classic morphologic features of Lymphoepithelioid lymphoma (Lennert lymphoma) with scattered cytotoxic T-cells admixed with numerous epithelioid histiocytes. While most Lennert lymphomas are either CD4 or CD8 positive, this case shows very unusual phenotype with the neoplastic T-cells double negative for CD4/CD8 and surface CD3. In addition, the neoplastic T-cells show weak expression of B-cell markers CD20 and OCT2. While they show expression of T follicular helper cell markers ICOS, PD1 and BCL6. The expression of PD1 and BCL6 are weak, and thus insufficient for diagnosis of nodal T follicular helper cell lymphoma.

Panel Diagnosis: PTCL-NOS lymphoepithelioid variant (Lennert lymphoma)

EA4HP26-LYWS-256**Primary Cutaneous T cell lymphoma with Granulomatous Features with Subsequent Nodal Lymphoepithelioid PTCL**

Dr. Maryam Sharifian¹, Dr. Achal Acharya¹, Dr. Imran Siddiqi²

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Case Description

A 72-year-old female presented with a history of a rash involving the right inner upper arm in 6/2022. She subsequently developed multiple maculonodular cutaneous lesions distributed diffusely without a specific pattern. No clinically enlarged lymph nodes were initially identified. Mycosis fungoides was suspected clinically. Empiric use of clobetasol was initiated with marked improvement of symptoms. A skin biopsy on 11/2023 demonstrated cutaneous T-cell lymphoma with granulomatous features. CT imaging demonstrated no evidence of systemic lymphoma. Additionally, other skin lesions with similar histopathology were treated with intralesional corticosteroids since 10/2022. Bexarotene was initially administered, followed by methotrexate and leucovorin along with phototherapy, and showed improvement in the patient's symptoms. On 11/23, left axillary lymphadenopathy was identified, and a core biopsy demonstrated extensive involvement by T-cell lymphoma.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings**Skin, Punch Biopsy (2023):**

H&E-stained sections demonstrate psoriasiform epidermal hyperplasia with prominent epidermotropism. The papillary dermis adjacent to the dermoepidermal junction shows a patchy lichenoid lymphocytic infiltrate. Within the reticular dermis, intermediate-sized atypical lymphocytes are admixed with numerous histiocytes, including multinucleated forms, in a diffuse interstitial and infiltrative pattern. Scattered eosinophils are present.

Lymph Node, Right Axillary, Core Biopsy (2024):

H&E-stained sections demonstrate complete effacement of nodal architecture by a diffuse atypical T-cell infiltrate composed of small- to medium-sized lymphoid cells with irregular and angulated nuclear contours. Numerous well-formed aggregates of epithelioid histiocytes forming small non-necrotizing granulomas are distributed throughout the node, accompanied by scattered eosinophils. No residual uninvolved nodal tissue is identified. Rare mitotic figures are present; however, necrosis and morphologic features of large cell transformation are not identified.

Immunophenotype

The atypical lymphocytes in both skin and lymph node express CD2, CD3, and CD5, with significant loss of CD7 expression and increased CD4:CD8 ratio (>10:1). EBV-encoded RNA (EBER) in situ hybridization is negative. CD30 highlights rare cells.

Cytogenetics

N/A

Molecular Studies

Identical clonal T-cell receptor gene rearrangements are detected in peripheral blood and skin, supporting a shared clonal T-cell population. T-cell clonality testing on the lymph node demonstrated detectable clonal T-cell receptor beta (TCRB) and/or gamma (TCRG) gene rearrangements by PCR analysis.

Proposed Diagnosis

Primary cutaneous T-cell lymphoma with granulomatous features and subsequent nodal lymphoepithelioid PTCL

Interesting Feature(s)

Granulomatous reactions are uncommon in peripheral T-cell lymphomas and may obscure the underlying neoplastic process, creating potential diagnostic pitfalls. Fewer than 100 cases of granulomatous mycosis fungoides have been reported in the literature. The patient's initial clinical presentation and skin biopsy were considered as granulomatous mycosis fungoides. Lymphadenopathy was not detected until more than 1 year following skin presentation, and subsequent lymph node biopsy showed features of lymphoepithelioid variant of PTCL, NOS (Lennert lymphoma). Accordingly, this case exemplifies the challenging differential diagnosis of granulomatous mycosis fungoides with subsequent lymph node involvement versus primary cutaneous presentation of Lennert lymphoma.

Panel Diagnosis: Granulomatous Mycosis Fungoides involving LN

Nodal T-cell follicular helper (TFH) lymphoma, angioimmunoblastic type (nTFHL-AI), with extensive granulomatous inflammation.

Dr. Carmen Lome-Maldonado¹, Dr. Ivonne Vazquez de las Heras¹, Dr. Xavier Ara-Mancebo¹, Dr. Andrea Molina-Alvarez¹, Dr. Natalia Papaleo², Dr. Barbara Tazón-Vega¹, Dr. Concepción Fernandez-Rodríguez¹, Yeinmy Castillo-Nuñez¹, Dr. Xavier Calvo-Gonzalez¹, Dr. Lluís Colomo¹

¹ Hospital del Mar, Pathology, Barcelona, Spain; ² Hospital de Sabadell Parc Tauli, Pathology, Sabadell, Spain

Case Description

A 65-year-old woman with a history of multiple allergies presented with leukocytosis (18,000/ μ L), absolute eosinophilia (1,040/ μ L), and monocytosis (780/ μ L). Peripheral blood flow cytometry detected a distinct atypical T-cell population (0.16%, CD3s-/CD4+), raising suspicion of a T-cell lymphoproliferative disorder. CT imaging revealed widespread supra- and infradiaphragmatic lymphadenopathy and splenomegaly. In December 2021, cervical lymph node biopsy confirmed nodal T-cell follicular helper (TFH) lymphoma, angioimmunoblastic type (nTFHL-AI), with a marked granulomatous response. Following CHOP14, only a partial response was achieved, and disease progression was documented three months later. After six cycles of GEMOX, the disease persisted with splenomegaly, suspected pleural infiltration, and progressive lymphadenopathy. A second biopsy in October 2022 confirmed the diagnosis. After transient stabilization with cyclophosphamide and prednisone, she enrolled in the ASTX660-03 (decitabine/cedazuridine) trial. A minimal partial response in June 2023 was followed by a rapid relapse with mammary gland infiltration, and the patient died three months later.

Biopsy Fixation Details

4% buffered formaldehyde.

Frozen Tissue Available

None.

Details of Microscopic Findings

All biopsies showed complete nodal effacement by a diffuse polymorphous infiltrate of medium-sized atypical T-cells with clear cytoplasm, admixed with eosinophils, plasma cells, and scattered large immunoblastic and some Reed–Sternberg-like (RS-like) cells. Prominent high endothelial venules and a striking granulomatous reaction rich in multinucleated giant cells partially obscured the neoplastic component; these features were also seen in the mammary gland biopsy.

Immunophenotype

Atypical T-cells were CD3+, CD5+, CD7+, CD4+++[AMX1] /CD8–, expressing TFH markers PD1 (strong/diffuse), focal positivity for BCL6, and CXCL13, with CD10– and GATA3+. R-S–like cells were CD30+, CD20–, CD79a–. CD21 highlighted expanded, disorganized follicular dendritic cell networks. ISH for EBER was negative.

Cytogenetics

Not available.

Molecular Studies

PCR confirmed clonal TCR-beta and TCR-gamma rearrangements; IgH was polyclonal. NGS identified:

- *RHOA*: c.50G>T, p.(Gly17Val); VAF 8.5%
- *TET2*: c.945del, p.(Gln317ArgfsTer30); VAF 22.4%
- *TET2*: c.2305C>T, p.(Gln769Ter); VAF 21.1%

Proposed Diagnosis

Nodal T-cell follicular helper (TFH) lymphoma, angioimmunoblastic type (nTFHL-AI), with extensive granulomatous inflammation.

Interesting Feature(s)

nTFHL-AI is an aggressive lymphoma with well-defined clinicopathologic and molecular profiles; however, its association with a prominent granulomatous reaction, as in this case, is rare and diagnostically challenging. Historically, these cases might have been recognized as Lennert T-cell lymphoma with a TFH phenotype. However, the concept of Lennert lymphoma as a distinct entity is not included in current classifications (WHO and ICC), which suggest recognizing the granulomatous response as a peculiar associated inflammatory pattern present in certain lymphoproliferative lesions. The coexistence of *RHOA* p.G17V and dual *TET2* mutations, combined with rapid clinical progression, reflects the adverse disease biology of the disease. Early detection of a small circulating atypical T-cell clone by flow cytometry highlights the value of this tool for early, non-invasive diagnosis of PTCL-THF presenting with circulating neoplastic cells (PMID 16572417, 35060668).

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-280

Nodal T follicular helper cell lymphoma, angioimmunoblastic type, with prominent lymphoepithelioid infiltrate

Dr. Christine Heisen¹, Dr. Alexander Craig¹, Dr. Sebastian Fernandez-Pol¹, Dr. Joshua Menke¹

¹ Stanford Medicine, Department of Pathology, Palo Alto, USA; ² Stanford Medicine, Pathology, Palo Alto, Germany

Case Description

29-year-old male presented with 6 months of progressive diffuse lymphadenopathy and hypercalcemia. Excisional biopsy of an inguinal node was performed. Outside pathologists initially favored Rosai-Dorfman disease and NLPHL pattern B before presentation at our institution for treatment. The case is reviewed in-house.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of lymph node show near-complete effacement of architecture replaced by prominent clusters of epithelioid histiocytes mimicking granulomatous inflammation and admixed small-to-medium sized mature lymphocytes with mild nuclear contour irregularities, with poorly defined residual atretic follicles and delicate vasculature. Only rare scattered larger immunoblast-like cells are noted. No increased mitotic activity, significant vascular proliferation, or necrosis is identified. AFB, GMS and FITE stains are negative.

Immunophenotype

Immunohistochemical stains show that most lymphocytes are CD3+ T-cells. The CD4:CD8 ratio is not markedly skewed, but a significant proportion of the T-cells express the T follicular helper markers PD-1 and ICOS. The T-cells are additionally positive for CD30 (~5%), PD1, CD7, TRBC1 (subset, no marked skew), TCR beta, GATA3 (dim, subset), CCR4 (subset), granzyme (subset) and perforin (subset); and negative for TCR delta, CD10, CXCL13, BCL6, TCL1, T-bet and TIA1. Histiocytes express CD15, BCL1, and S100 (subset). CD19, CD20, PAX5, CD79a, OCT2 highlight rare, scattered background B cells in a vaguely nodular pattern, subset of which express IgD and TCL1. Kappa and lambda IgG by ISH shows rare polytypic plasma cells. EBER and Merkel cell polyomavirus by ISH are negative. CD21 highlights expanded, disrupted follicular dendritic cell networks.

Flow cytometry identified 93% T-cells with normal CD4:CD8 ratio and normal pan T-cell antigen expression, as well as 6% polytypic B-cells; no aberrant lymphoid population was identified.

Cytogenetics

N/A

Molecular Studies

T and B cell receptor gene rearrangements by NGS revealed clonal T-cell receptor beta and gamma chain gene rearrangements and no B-cell receptor gene rearrangement. Mutation profiling by targeted NGS (HemeSTAMP; 203 genes) revealed an intergenic region::VAV1 fusion.

Proposed Diagnosis

Nodal T follicular helper cell lymphoma, angioimmunoblastic type (nTFHL-AI), with prominent lymphoepithelioid infiltrate

Interesting Feature(s)

The morphologic findings raise a wide differential, including reactive/infectious or neoplastic histiocytic processes, NLPHL (pattern B; T-cell/histiocyte rich pattern), PTCL NOS lymphoepithelioid variant (Lennert lymphoma [LeL]). Immunophenotyping reveals mature CD3+ T-cells with normal CD4:CD8 ratio and TFH phenotype (PD1+, ICOS+) in a background of expanded follicular dendritic cell meshworks, scattered polytypic B, and rare plasma cells. Though the histologic features resemble LeL, the WHO 5th edition recommends that lymphomas with lymphoepithelioid morphology and TFH immunophenotype be classified as nTFHL based on prior studies showing similar prognoses for TFH+ cases of LeL and nTFHL-AI, which are both less favorable than TFH- cases of LeL. Expanded FDC networks additionally support nTFHL-AI over LeL. Thus, the diagnosis of nTFHL-AI was rendered, supported by the presence of TCR gene rearrangements and VAV1 fusion. Prior misdiagnoses highlight the difficulty of diagnosis.

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-284

Peripheral T cell lymphoma (Lennert lymphoma) with an unusual phenotype and associated EBV viremia

Dr. Kavya Penmethsa, Dr. Georgi Lukose, Dr. Cole Miller, Dr. Madhu Ouseph, Dr. Amy Chadburn

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Case Description

An 87-year-old female with a history of hypertension, type 2 diabetes and peripheral vascular disease presented with a lower extremity ulcer. Prior to presentation she had had months of intermittent fevers and progressive fatigue. Imaging studies identified lymphadenopathy above and below the diaphragm and splenomegaly. Peripheral blood flow cytometry showed a small abnormal T-cell population. Laboratory studies were significant for normal WBC, Hgb 6.8g/dL, platelets 101K/uL, LDH 353U/L (high) and an EBV viral load of >190K cpy/mL. Bone marrow and right inguinal lymph node biopsies were performed.

Biopsy Fixation Details

Bone marrow core: Bouins; Lymph node: 10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Bone marrow: Histologic sections show a hypercellular marrow (80%) with an extensive interstitial and diffuse lymphohistiocytic infiltrate containing small to intermediate-sized atypical lymphocytes, eosinophils and some plasma cells. Scattered multinucleated giant cells, but no large lymphoid cells or Reed-Sternberg cells are identified. Trilineage hematopoiesis is seen.

Lymph node: Histologic sections show architectural effacement by a lymphohistiocytic proliferation consisting of numerous epithelioid histiocytes, small lymphocytes and medium-sized lymphocytes with mild nuclear irregularity. Rare large atypical lymphocytes, plasma cells and rare eosinophils are seen. No necrosis is seen. The lymphohistiocytic infiltrate extends into perinodal fat.

Immunophenotype

Bone marrow: The lymphoid infiltrate is composed largely of CD3-positive T cells expressing CD2, CD5, CD8, and ICOS (subset), with decreased expression of CD7, and lack expression of CD4, CD30, BCL6, and PD1. In situ hybridization for EBV-encoded-small RNAs (EBER) shows rare positive lymphocytes.

Lymph node: The lymphoid infiltrate is composed largely of CD3-positive T cells with a predominance of CD8-positive T cells which co-express TIA-1, granzyme B, GATA3, CD25, FOXP3 and PD1 (weak partial) and lack expression of CD30, TBX21 (T-bet), MUM1 and BCL6. A subset of cells appear to have decreased expression of CD7. The proliferation rate (KI67) is ~20%. CD20, PAX5, CD79a show rare residual B-cell follicles; CD21, CD23 highlight small atrophic follicular dendritic cell meshworks. In situ hybridization for EBER shows rare positive small lymphocytes.

Cytogenetics

46,XX[20]

Molecular Studies

Bone marrow: TCRG gene rearrangement: oligoclonal. IGH and IGK gene rearrangement: polyclonal.

Lymph node: TCRG gene rearrangement: clonal in a polyclonal background. IGH and IGK gene rearrangement: polyclonal.

Proposed Diagnosis

Peripheral T-cell lymphoma, NOS, lymphoepithelioid lymphoma (Lennert lymphoma)

Interesting Feature(s)

This is a relatively rare CD8-positive Lennert lymphoma. This case falls into the PTCL-TBX21 category, based on the phenotypic profile: TBX21 negative, CXCR3+, GATA3+, CCR4+, a less aggressive category of PTCL. This histogenic category correlates with polymorphic cellular infiltrates (associated tumor microenvironment; TME) as seen in our case. The neoplastic cells in our case express TFH markers in addition to cytotoxic markers. TFH expression in cytotoxic TBX21 cases is associated with more aggressive disease. The patient also presented with EBV viremia. The impact of this finding is not clear but could influence the TME composition and, as suggested by others, prognosis. Unfortunately, our patient was lost to follow-up 2 months after diagnosis and thus the clinical behavior of her disease cannot be assessed.

Panel Diagnosis: nTFHL

EA4HP26-LYWS-295

Peripheral T-cell lymphoma, not otherwise specified, lymphoepithelioid variant (Lennert's lymphoma)

Dr. Tran B. Nguyen¹, Dr. Sergio Pina-Oviedo¹, Dr. Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

¹ Duke University School of Medicine, Department of Pathology, Durham, USA; ² Duke Cancer Institute, Durham, USA

Case Description

The patient is a 77-year-old woman with a history of hypercalcemia and acute kidney injury who presented with imaging obtained to look for a cause of hypercalcemia, and revealed splenomegaly and supraclavicular/axillary lymphadenopathy. Complete blood counts showed WBC 5.6x10⁹/L, Hgb 9.6 g/dL, PLT 191x10⁹/L. She underwent an excisional biopsy of the right axillary lymph node. After the final diagnosis, she received six cycles of mini-CHOP chemotherapy. At the last follow-up, she demonstrates no evidence of disease.

Biopsy Fixation Details

Sections of the lymph node were fixed in formalin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Touch preps consist of a polymorphic infiltrate of atypical lymphoid cells, mostly small with few scattered large forms. Tissue sections consist of a lymph node with complete effacement of the nodal architecture by a polymorphic lymphomatous infiltrate composed of small mature-appearing lymphocytes, scattered large atypical lymphoid cells with clear cytoplasm and numerous epithelioid macrophages. The lymphoma cells have moderately condensed chromatin and irregular nucleus.

Immunophenotype

The lymphoma cells are positive for CD3, CD7, CD2 (variable), CD4 (subset), CD8 (subset), CD5 (variable), and CD30 (small subset <5%), and are negative for CD20, PAX5, CD21, CD10, BCL-6, PD1, and ALK. CD21 highlights residual follicular dendritic cell meshwork without expansion of meshworks. CD20 and PAX5 highlight few scattered residual lymphoid aggregates, mostly "pushed" to the periphery, as well as a few scattered small B-cells. CD4 highlights the epithelioid macrophages (weak labelling as compared to the lymphoma cells). BCL-6 is also positive in a subset of macrophages. The Ki-67 proliferation index is ~25-30%. EBER ISH is negative.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Peripheral T-cell lymphoma, not otherwise specified, lymphoepithelioid variant (Lennert's lymphoma)

Interesting Feature(s)

- Lennert lymphoma (lymphoepithelioid lymphoma) represents a rare morphologic variant of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), characterized by a prominent admixture of small to medium-sized neoplastic T cells and numerous epithelioid histiocytes. Clinically, this entity may present with systemic manifestations and metabolic derangements, including hypercalcemia. Recognition of these systemic features is important, as they may be the initial clue to an underlying lymphoproliferative disorder and can contribute significantly to morbidity at presentation.
- Adequate tissue sampling via excisional lymph node biopsy is critical for accurate diagnosis, as the defining histologic feature of Lennert lymphoma is the striking epithelioid histiocytic background, which may be difficult or impossible to appreciate in small core or needle biopsy specimens.

Panel Diagnosis: PTCL-NOS lymphoepithelioid variant (Lennert lymphoma)

EA4HP26-LYWS-298

EBV(+) lymphoma with abundant Reed-Sternberg-like cells, favor T-cell lymphoma. Numerous hemophagocytic histiocytes, supporting a concomitant diagnosis of hemophagocytic lymphohistiocytosis (HLH).

Dr. Tran B. Nguyen¹, Dr. Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

¹ Duke University School of Medicine, Department of Pathology, Durham, USA; ² Duke Cancer Institute, Durham, USA

Case Description

The patient is a 72-year-old man with a history of prostate cancer status post transurethral resection of the prostate ten years prior, transient ischemic attack/cerebrovascular accident, chronic obstructive pulmonary disease, hypertension, and hyperlipidemia, who presented with a two-month history of progressive weight loss, night sweats, fever, and fatigue. He was found to have pancytopenia and splenomegaly. Imaging demonstrated diffuse hypermetabolic lymphadenopathy and increased FDG avidity within the bone marrow. Complete blood counts

revealed a white blood cell count of $1.5 \times 10^9/L$, hemoglobin of 8.7 g/dL, and platelet count of $57 \times 10^9/L$. Serum ferritin was markedly elevated at 4,524 ng/mL (reference range 7–91 ng/mL). The patient underwent a bone marrow biopsy and met diagnostic criteria for hemophagocytic lymphohistiocytosis. Despite diagnosis, the patient's clinical condition rapidly deteriorated with progression to multiorgan failure, including oliguric renal failure, and he subsequently died.

Biopsy Fixation Details

The bone marrow core biopsy was fixed in acetic zinc formalin, followed by HCl-based decalcification.

Frozen Tissue Available

Not available

Details of Microscopic Findings

The bone marrow is hypercellular (approximately 50%) with 2% blasts. Numerous histiocytes with phagocytosed granulocytes and erythroid precursors are readily identified. Rare giant cells with enlarged nuclei and very prominent nucleoli are present. The core biopsy also demonstrates sheets of hemophagocytic histiocytes interspersed with large atypical lymphoid cells and large bizarre cells with Reed-Sternberg-like morphology. These areas additionally contain scattered plasma cells and eosinophils.

Immunophenotype

CD3 highlights numerous atypical lymphocytes, associated with densely clustered histiocytes and Reed-Sternberg-like cells, which are CD2(+), CD4(abundant histiocytes and scattered lymphocytes), CD5(+), CD7(subset+), CD56(scattered positive cells), TIA-1(scattered positive cells), and Granzyme B(scattered positive cells). Reed-Sternberg-like cells are positive for CD30, CD15(variably+), PAX-5(weakly+), EBER in-situ hybridization; and negative for CD2, CD3, CD20, and ALK-1. CD68 and CD163 stain abundant hemophagocytic histiocytes.

Cytogenetics

Normal male karyotype 46,XY[19]

Molecular Studies

Clonality: A monoclonal T-cell population was detected by TCR beta chain PCR. TCR gamma is negative.

Proposed Diagnosis

EBV(+) lymphoma with abundant Reed-Sternberg-like cells, favor T-cell lymphoma. Numerous hemophagocytic histiocytes, supporting a concomitant diagnosis of hemophagocytic lymphohistiocytosis (HLH).

Interesting Feature(s)

- This case illustrates a critical diagnostic pitfall, as the presence of EBV-positive Reed-Sternberg-like cells may lead to an initial impression of classical Hodgkin lymphoma.
- Integration of morphology, immunophenotype, and molecular clonality studies is essential to avoid misclassification and to recognize underlying T-cell lymphoma. EBV-positive T-cell lymphomas can closely mimic classical Hodgkin lymphoma, particularly when Reed–Sternberg–like cells are prominent.
- The coexistence of EBV-positive T-cell lymphoma and HLH portends a very poor prognosis, with high early mortality, emphasizing the need for rapid diagnosis and consideration of aggressive therapies when feasible.

Panel Diagnosis: PTCL-NOS with RS-like cells associated with HLH

Pancytopenia in a Patient with History of Chronic Lymphocytic Leukemia

Dr. Zhihong Hu¹, Dr. Andres Ernesto Quesada², Dr. Wei Wang², Dr. Sa A. Wang²

¹ The University of Texas MD Anderson Cancer Center, Department of Laboratory Medicine, Houston, USA; ² The University of Texas MD Anderson Cancer Center, Department of Hematopathology, Houston, USA

Case Description

A 65-year-old man with a history of chronic lymphocytic leukemia (CLL), initially diagnosed in 2020 and managed with observation, was started on acalabrutinib in 2025 and treated for approximately three months. Therapy was discontinued three weeks prior to presentation because of pancytopenia. He was referred to MDACC for further management on 12/24/2025. Peripheral blood (PB) flow cytometry performed on 12/25/2025 demonstrated very low-level residual CLL. A bone marrow (BM) biopsy performed on 12/29/2025 showed extensive necrosis with very low-level aberrant small B cells co-expressing CD5 by flow cytometry. On 1/6/2026, the complete blood count revealed pancytopenia. Markedly elevated inflammatory markers were present, including soluble interleukin-2 receptor (CD25) at 17,611.7 pg/mL, interleukin-10 at 4,229.1 pg/mL, and ferritin >97,000 ng/mL. Triglyceride: 421; D-dimer increased, and fibrinogen decreased. Liver transaminase increased.

Biopsy Fixation Details

Fixation: 3 hours in 10% neutral buffered formalin; Decalcification: 12 hours in 5% formic acid.

Frozen Tissue Available

Not performed.

Details of Microscopic Findings

PBS review on 1/6/2026 demonstrated pancytopenia with rare large atypical lymphoid cells exhibiting irregular nuclear contours, some with cytoplasmic granules. BM biopsy (1/6/2026) revealed extensive involvement by a malignant lymphoid infiltrate. The malignant cells were large with irregular nuclei, variably prominent nucleoli, and scant to moderate cytoplasm. Trilineage hematopoiesis was markedly decreased. Immunohistochemical studies on the BM core biopsy showed the malignant cells positive for CD3, CD56, TIA-1, and Granzyme B, and negative for CD5, CD7, CD20, CD23, CD34, cyclin D1, PAX5, and EBER-ISH.

Immunophenotype

Flow Cytometry (bone marrow, 1/6/2026) identified an abnormal population T-cell population with larger cell size representing approximately 3.5% of total events and showed the following immunophenotype: CD45⁺, CD2⁺, CD3⁺; CD4⁻, CD5⁻, CD7⁻; CD8 partially positive (small subset); CD10⁻, CD16⁻, CD25⁺, CD26⁺, CD30⁻; CD52⁺, CD56⁺, CD57⁻; CD94 partially positive; TCR αβ negative, TCR γδ positive, TRBC1 negative. Additionally, a very small population of aberrant B cells (0.19% of total events) with CD5 co-expression, immunophenotypically consistent with residual CLL, was detected.

Cytogenetics

Result pending.

Molecular Studies

Results pending.

Proposed Diagnosis

Gamma/Delta T-cell lymphoma, extensively involving a partially necrotic bone marrow.

Measurable residual chronic lymphocytic leukemia detected by flow cytometry.

Interesting Feature(s)

This case highlights a rare occurrence of γδ T-cell lymphoma arising in a patient with antecedent CLL treated with acalabrutinib. We postulate that CLL-associated immune dysfunction, characterized by impaired immune surveillance and defects in both innate and adaptive immunity, may have facilitated the emergence and expansion of a malignant γδ T-cell clone. The γδ T-cell lymphoma was further complicated by the development of

hemophagocytic lymphohistiocytosis (HLH), resulting in a highly complex and clinically challenging presentation. Although bone marrow findings in HLH typically include increased lymphocytes and histiocytes with stress hematopoiesis, in rare instances HLH may be associated with extensive bone marrow necrosis, which can obscure the underlying pathology. In patients presenting with HLH, it is essential to thoroughly evaluate for an underlying T-cell lymphoma, regardless of clinical circumstances.

Panel Diagnosis: gd TCL with HLH

EA4HP26-LYWS-312

Fulminant Case of ALK+ Anaplastic Large Cell Lymphoma

Dr. Nicolas Lopez-Hisijos, Dr. Claudio Mosse

Vanderbilt University Medical Center, Nashville, USA

Case Description

- 28-year-old woman with a complicated medical history
- Klippel-Feil syndrome:
- Congenital disease characterized by cervical vertebrae fusions, scoliosis, meningoceles, and diastematomyelia (split cord)
- Chronic Pain:
- Associated with congenital disease requiring long history of surgical and medical intervention
- Severe migraine-type headaches recalcitrant to treatment
- Family history of rheumatoid arthritis:
- Joint pain: seronegative and not considered to be related to autoimmune etiologies
- Renal insufficiency
- Thought to be related to congenital syndrome, recurrent large calculi with hydronephrosis
- Presented to ED for acute abdominal pain, fever and night sweats
- Imaging showed diffuse lymphadenopathy
- Marked thickening of bowel wall
- Enlarged sacral meningocele with enhancement on PET

Biopsy Fixation Details

- Duodenal biopsy and ascitic fluid cell block fixed with neutral buffered 10% formalin and paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

- The cytology showed large atypical cells with anaplastic morphology
- Cells with similar morphology were seen in the lamina propria and lymphatic spaces of the duodenal biopsy

Immunophenotype

- The large neoplastic cells were positive for CD30, CD5, ALK (strong nuclear and cytoplasmic), and granzyme. CD4 showed weak partial labeling.
- Background was mostly composed of small T-cells
- The neoplastic cells were negative for CD2, CD3, CD8, CD20, PAX5, and EBER

Cytogenetics

No

Molecular Studies

No

Proposed Diagnosis

- Anaplastic large cell lymphoma- ALK positive

Interesting Feature(s)

- The patient was diagnosed with ALK+ ALCL and promptly treated with CHP
- During the first cycle, she developed acute respiratory failure and expired
- Autopsy showed disseminated disease, including large tumor nodules in both lungs
- ALK+ ALCL is thought to have a relatively good prognosis, especially in young patients
- This patient had systemic imaging often due to her congenital condition and the associated pain syndromes. A CT of the abdomen and pelvis 3 months prior to her presentation at the ED did not show lymphadenopathy or GI wall thickening. Also, she did not report B-symptoms until her final presentation.
- Therefore it is reasonable to consider this case as a highly aggressive presentation of this disease.
- We do not have molecular data, unfortunately.

Panel Diagnosis: ALK+ ALCL

EA4HP26-LYWS-315

Pediatric T-cell Lymphoma (ALCL or SMARCB1 deficient?)

Dr. Nicolas Lopez-Hisijos

Vanderbilt University Medical Center, Nashville, USA

Case Description

- 2-year-old girl who presented to the pediatrician with a rapidly enlarging neck mass and recent onset of B-symptoms (fever, appetite loss, night sweats)
- Imaging showed a large mass centered in the mediastinum (8.1cm)
- An excisional biopsy was requested
- After extensive diagnostic work-up the patient was treated with SOC+BV (alternating courses of cytotoxic chemo and brentuximab)
- Achieved complete remission after treatment

Biopsy Fixation Details

- Biopsy of mediastinal mass: fixed in neutral buffered 10% formalin and embedded in paraffin

Frozen Tissue Available

No

Details of Microscopic Findings

- The excisional biopsy of the mediastinal mass appeared to be either a lymph node or an aggregate of lymphoid cells infiltrating soft tissue
- There was no thymic tissue present
- The lymphoid infiltrate was arranged in a vaguely nodular pattern and it was composed mostly of small lymphocytes and histiocytes. Rare large cells were present, with immunoblastic morphology

Immunophenotype

- There was a population of CD30 positive cells with a range in size (medium to large)
- These cells were also positive for CD2, CD4 (partial), and negative for CD7, CD3, CD5, CD8, granzyme, perforin, CD20, PAX5, TdT, CD34, CD10, CD1a, MPO, CD177, CD33
- INI (SMARCB1) was performed at a consulting institution and reported to be partially lost in the tumor cells
- We were not able to review that slide

Cytogenetics

No

Molecular Studies

- TCR rearrangement PCR: negative
- NGS panel of >600 genes (hematolymphoid panel): negative
- RNA seq fusion analysis: negative

Proposed Diagnosis

- Anaplastic large cell lymphoma – ALK negative

Interesting Feature(s)

- The diagnosis of ALCL- ALK negative in children is extremely rare
- Clinically the diagnosis of a lymphoid malignancy was high on the differential, but given the age of the patient and the location of the tumor, T-ALL was the top diagnostic consideration
- Given the rarity of the diagnosis we consulted with an outside institution
- Based on the partial INI loss seen on IHC, they mentioned the possibility of this being a T-cell lymphoma with SMARCB1 loss (PMID: 33163846; PMID: 39362842)
- This consideration seemed difficult for us to prove, given that the NGS panel performed included SMARCB1 for sequencing and RNA sequencing did not show any abnormalities
- Most of the reported cases of SMARCB1 deficient T-cell lymphoma showed that promoter-silencing via hypermethylation is the cause for silencing (which we did not evaluate)
- The patient responded very well to treatment and is currently in CR

Panel Diagnosis: PTCL with INI/SMARCB1-deficient loss

EA4HP26-LYWS-334

A rare and aggressive entity: CD30/CD56/CD8-positive primary bone marrow T-cell lymphoma associated with EBV infection and HLH

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Case Description

A 33-year-old Egyptian man with a history of treated hepatitis C and schistosomiasis presented with persistent fever, cough, pancytopenia, febrile neutropenia, and hepatosplenomegaly. Sepsis was ruled out; ferritin levels continued to rise, EBV load was elevated (20,369 IU/mL), and imaging indicated pneumonia. PET/CT showed extensive bone marrow involvement, meeting HLH diagnostic criteria.

Biopsy Fixation Details

The trephine biopsy was formalin-fixed, paraffin-embedded, and decalcified using standard laboratory protocols.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Peripheral blood reveals marked pancytopenia. The BM aspirate is significantly hemodilute with scattered small lymphocytes including some atypical forms. Touch imprint showed many mature looking small to medium lymphoid cells with few scattered abnormal large sized cells with pleomorphic nucleus. BM biopsy is markedly hypercellular (almost 100% cellularity) with infiltration by highly pleomorphic abnormal cells of varying size, including pleomorphic cells with multilobated nuclei and hallmark cells with horseshoe nuclei. These cells reside within a background

composed of small lymphocytes, histiocytes and few plasma cells, and numerous macrophages (some with hemophagocytosis). Fibrosis is increased (grade 2–3/3).

Immunophenotype

IHC: The abnormal cells are positive for CD45, CD2, CD8, CD30, CD25, Granzyme B, CD56 and some are positive for CD7. The cells are negative for CD20, PAX5, CD79, CD3, CD5, CD4, ALK, CD10, EBER, BCL6 and PD1. The background lymphocytes are composed mostly of CD4-positive cells. CD68 immunostain highlights remarkable increased histiocytes/macrophages.

Cytogenetics

Failed culture.

Molecular Studies

Inconclusive: TCR gene rearrangement did not amplify sufficiently to produce an interpretable result.

Proposed Diagnosis

CD30/CD56/CD8-positive primary bone marrow T-cell lymphoma associated with EBV infection and HLH

Interesting Feature(s)

This case is notable for its rare presentation with primary BM involvement, aggressive course and challenging classification due to overlapping immunophenotypic features. CD56-positive, CD30-positive large T-cell lymphoma is rare and complex. The overlapping immunophenotype in this lymphoma between different entities further complicates the diagnosis. The main differential diagnoses are anaplastic large cell lymphoma (ALCL) and extranodal NK/T-cell lymphoma subtypes. ALCL typically shows strong CD30 expression and lacks most T-cell markers; while most cases are CD4 positive, a minority are CD8 positive, that tend to follow a more aggressive course. CD56 positive ALCL is associated a higher incidence of bone involvement and poor prognosis.

Panel Diagnosis: PTCL, CD30 with HLH

EA4HP26-LYWS-340

A syncytial CD30+ lymphoma

Dr. Léna Mescam¹, Dr. Florian Pesce¹, Dr. Emeline Durieux¹, Prof. Luc Xerri^{1,2}

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Case Description

A 77 years-old man , treated 2 years before for a locally advanced lung epidermoid carcinoma (immuno/chemotherapy), presents a slowly growing left axillary hypermetabolic lymph node.

Biopsy Fixation Details

Formalin 4%.

Frozen Tissue Available

No

Details of Microscopic Findings

The lymph node resection shows a destruction of the lymph node by a nodular sclerosing and necrotic proliferation. This nodules are represented by central necrosis with numerous eosinophils, surrounded by palisading sheets of large pseudo cohesive atypical cells , with a syncytial pattern. These cells are large and pleomorphic with lobated vesicular nuclei and prominent nucleoli, corresponding to Hodgkin/ Reed-Sternberg features, associated with hallmark cells with horseshoe-shaped nuclei, multiple nucleoli, and abundant amphophilic cytoplasm.

Histiocytes and eosinophils are numerous in these tumour sheets, rimmed by abundant plasma cells.

Immunophenotype

Large atypical cells are :

- positive for CD30+++, CD15 (focal), CD45 (weak), EMA (focal), MUM1, CD4+/- (?), PDL1++, GATA++, Bcl6 +/-, MYC +/-

- negative for CD20, PAX5, CD79a, PU1 (numerous histiocytes), BOB1, OCT2, CD3, CD2, CD5, CD7, CD8, CD43, cytotoxicity markers (Perforine, Granzyme B, Tia1), TRBC1, TCR delta, ALK, LEF1, STAT6, CD10, CD138, PD1, HHV8, CKAE1-AE3, LMP1, EBNA2,

Negativity of HIS EBER and HIS Kappa/Lambda

Additional markers IHC : TCR alpha+/TCR delta -, p63+

Cytogenetics

FISH TP63 and DUSP22 : ongoing.

Molecular Studies

- o Clonality analysis : no B clone , oligoclonal T profile.
- o NGS : ongoing

Proposed Diagnosis

ALK-negative, anaplastic large cell lymphoma,

Syncytial pattern / pseudo classical Hodgkin lymphoma

Interesting Feature(s)

- **Syncytial pattern /pseudo classical Hodgkin lymphoma** with :

- sheets of large atypical CD30+ cells
- within sclerosing nodules
- Hodgkin-like, RS-like and anaplastic cells
- associated with histiocytes and eosinophils
- around necrotic areas

- Unusual phenotype :

T markers negative : CD2-, CD3-, CD5-, CD7-, also CD43-, only CD4+/-

no cytotoxicity (perforine -, Tia1 -, Granzyme B -)

TCR alpha+ : TCR staining is of great value in this case.

Panel Diagnosis: ALK-ALCL with a syncytial pattern

EA4HP26-LYWS-341

Nodal T follicular helper cell lymphoma, angioimmunoblastic type, with prominent clusters of epithelioid histiocytes.

PhD/MD Natalia Papaleo¹, Ricard Onieva Carbajo¹

¹ Parc tauli university hospital, Pathology, Barcelona, Spain; ² Universitat autònoma de Barcelona, Barcelona, Spain

Case Description

A 70-year-old man with a medical history notable only for pleuritis in his youth, hypertension and dyslipidaemia, was referred for evaluation of lymphadenopathies of one month's duration, associated with arthralgia. Laboratory investigations revealed a leukocyte count of $5.88 \times 10^9/L$, haemoglobin 116 g/L, and an elevated lactate dehydrogenase of 327 U/L. SARS-CoV-2 PCR was positive.

PET-CT imaging demonstrated a metabolically active lymphoproliferative process with widespread supra- and infra-diaphragmatic lymphadenopathy, as well splenomegaly and osseous involvement.

Inguinal lymph node biopsy confirmed nodal T follicular helper cell lymphoma, angioimmunoblastic type (nTFHL-AI), with prominent clusters of epithelioid histiocytes. The patient was treated with CHOP, achieving only a partial

response. Disease progression occurred three months later, and subsequent salvage therapies with GEMOX followed by ESHAP failed to achieve durable disease control. The patient died 18 months after diagnosis.

Biopsy Fixation Details

4% buffered formaldehyde.

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic examination revealed complete effacement of the lymph node architecture by a polymorphous cellular infiltrate consisting of medium-sized T-cells with mild nuclear atypia admixed with reactive small lymphocytes, immunoblasts, Reed–Sternberg–like cells, plasma cells, and eosinophils. Abundant clusters of epithelioid histiocytes and prominent high endothelial venules were identified.

Immunophenotype

The atypical T cells were CD3⁺ and CD5⁺, with partial loss of CD7 and a CD4⁺/CD8[−] phenotype. They express TFH markers including PD-1, BCL6, CD10, ICOS, and focal CXCL13 positivity. Reed–Sternberg–like cells were CD30⁺ and negative for CD20. CD21 highlighted expanded follicular dendritic cell networks. In situ hybridization for EBER was positive in some cells.

Cytogenetics

None

Molecular Studies

PCR analysis confirmed clonal rearrangements of TCR-β and TCR-γ, while IgH showed a polyclonal pattern. Next-generation sequencing identified a RHOA mutation (c.50G>T, p.Gly17Val) with a variant allele frequency (VAF) of 3.9%.

Proposed Diagnosis

Nodal T follicular helper cell lymphoma, angioimmunoblastic type (nTFHL-AI), with prominent clusters of epithelioid histiocytes.

Interesting Feature(s)

nTFHL-AI is a neoplasm of mature T-cells characterized by a TFH phenotype, with recurrent *RHOA* mutations identified in approximately 70% of cases. Enhanced T-cell receptor signaling conferred by the *RHOA* mutation in naïve CD4⁺ T cells may promote their preferential TFH differentiation and dysregulated immune response. These mutations are rarely observed in peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).

Prominent clusters of epithelioid histiocytes may mimic a reactive granulomatous process as a differential diagnosis, or even the lymphoepithelioid (Lennert-like) variant of PTCL-NOS, a distinctive entity which may also exhibit a TFH cell phenotype (Hartmann, S et al. Histopathology 2011; Ondrejka, S et al. Virchows Archiv 2023)

The constellation of morphologic, immunophenotypic, and molecular features of this case is considered characteristic of nTFHL-AI in which Lennert like features has been described in this type of lymphoma.

Panel Diagnosis: NO POWERPOINT -CASE NOT REVIEWED

EA4HP26-LYWS-345

NODAL T-FOLLICULAR HELPER CELL LYMPHOMA, ANGIOIMMUNOBLASTIC TYPE, WITH HODGKIN-LIKE CELLS

Dr. Aneeza Irfan, Dr. Jie Xu, Dr. Francisco Vega, Dr. L. Jeffrey Medeiros, Dr. Jeong Hee Cho-Vega

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Case Description

•The patient, who is a 57-year-old man with no significant past medical history, presented with a one-month history of dyspnea, loss of appetite, fatigue, and low-grade fevers following an episode of streptococcal pharyngitis. • CT scan showed mediastinal, hilar, bilateral supraclavicular, left axillary, and retropectoral lymphadenopathy and splenomegaly (13.9cm)

. There was no known history of immunocompromise.

A pathologist from another laboratory rendered a diagnosis of classic Hodgkin lymphoma based on a lymph node excisional biopsy specimen. The case was reviewed at MDACC. Two subsequent lymph node core needle biopsy specimens were later performed at MDACC.

Biopsy Fixation Details

Formalin Fixed Paraffin embedded tissue

Frozen Tissue Available

Not available

Details of Microscopic Findings

The overall morphological features are similar in both external excised lymph nodes and later core needle biopsies. The excised enlarged lymph nodes in which normal architecture is extensively replaced by lymphoma. The neoplasm has a diffuse pattern and is composed of numerous small lymphoid cells, many of which have slightly irregular nuclear contours and pale cytoplasm, associated with histiocytes, eosinophils and scattered or loosely clustered large Hodgkin-like cells including a few that mimic Reed-Sternberg cells. There are also focal band-like fibrosis and areas of vascular proliferation.

Immunophenotype

The overall immunophenotype is same in both external excised lymph node and core needle biopsy samples.

The infiltrating atypical small lymphocytes are predominantly CD3+ T cells with a marked increase in CD4:CD8 ratio. CD7 is retained.

The lymphoma cells are positive for ICOS (80%), CXCL13 (partial), TCR β F1, and TRBC1 and negative for CD30, PD-1, CD56, CD10, BCL6, and TCR δ . T-cell rosettes around the large lymphoma cells are not identified.

HRS-like cells are also positive for CD30 (weak), PAX5 (weak or negative) and CD15 (minor subset). They are negative for CD45, CD20, OCT2, and CD3.

In situ hybridization for Epstein–Barr virus encoded RNA (EBER) is negative.

Flow cytometry is negative for aberrant B- or T-cell population.

Cytogenetics

Normal Male Karyotype

Molecular Studies

PCR-Based Clonality Assay

Low-level monoclonal TRG rearrangements in an oligoclonal background

TRB rearrangement is polyclonal.

Monoclonal IGH rearrangements

Next generation sequencing: Negative for somatic mutations

Proposed Diagnosis

NODAL T-FOLLICULAR HELPER CELL LYMPHOMA, ANGIOIMMUNOBLASTIC TYPE (nTFHL-AI), WITH HODGKIN/REED-STERNBERG-LIKE CELLS

Interesting Feature(s)

- A rare entity, with relatively few cases reported to date
- A subtype of nodal T-cell lymphoma with a T-follicular helper (TFH) phenotype, closely aligned with angioimmunoblastic T-cell lymphoma (AITL), in the WHO-HAEM5 and ICC classifications
- Characterized by expression of TFH markers (e.g., PD1, CXCL13, ICOS), distinct molecular signatures, and the presence of HRS-like cells, which are often EBV-positive, complicating diagnosis
- Cases can be initially misdiagnosed as classic Hodgkin lymphoma because of overlapping morphologic and immunophenotypic features with HRS-like cells
- Accurate classification is critical, as the treatment for nodal TFH lymphoma, angioimmunoblastic type, differs

significantly from that for Hodgkin lymphoma

- Excisional biopsy provides superior diagnostic yield compared with needle core biopsy
- Comprehensive IHC + molecular studies improve accuracy

Panel Diagnosis: nTFHL/TFHL with HRS-like cells

EA4HP26-LYWS-349

Peripheral T-Cell Lymphoma, NOS With Prominent Granulomatous Inflammation: A PTCL-TBX21 (TH1) Biologic Subtype Mimicking Sarcoidosis

Dr. Catalina Amador

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Case Description

A 71-year-old man presented with progressive shortness of breath and generalized weakness and was found to have widespread lymphadenopathy. PET/CT demonstrated bulky nodal disease involving paratracheal, periportal, and portocaval regions, with the largest node measuring 9.3 cm. An initial lymph node biopsy at an outside institution (slides unavailable) was interpreted as non-necrotizing granulomas consistent with sarcoidosis, and the patient was treated with prednisone, with only modest symptomatic improvement. Cardiac imaging showed no evidence of cardiac sarcoidosis. Given persistent symptoms and diagnostic uncertainty, he was referred for further evaluation. An excisional lymph node biopsy demonstrated PTCL-NOS. Staging revealed advanced disease with diffuse marrow-replacing abnormalities on spinal MRI, and serum LDH was elevated. CHOP chemotherapy was initiated; however, during the first cycle, the patient developed profound cytopenias complicated by a severe perirectal abscess and sepsis, and he died shortly thereafter.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Histologic sections show effacement of lymph node architecture by proliferation of medium-sized lymphoid cells with irregular nuclear contours. The background is notable for prominent, large, well-formed non-necrotizing granulomas.

Immunophenotype

Immunostains show that the neoplastic cells are positive for CD3, CD4, CD2, CD5, BF1, GATA3 (~80%), and CXCR3 (~80%), with aberrant loss of CD7 and partial aberrant CD20 expression, and negative for CD10, BCL6, PD1, ICOS, TCR-GD, CD30, TBX21, and EBER in situ hybridization. AFB and GMS stains are negative. Flow cytometry confirms a clonal CD4+ T-cell population with partial CD20 expression, TCRBC1 restriction, and loss of CD7; B cells are polyclonal.

Cytogenetics

Not performed

Molecular Studies

Clonal TCR γ/β gene rearrangements (PCR)

Proposed Diagnosis

Peripheral T-cell lymphoma, not otherwise specified, PTCL-TBX21 biologic subtype, with associated non-necrotizing granulomas

Interesting Feature(s)

This case illustrates how PTCL-NOS may present with prominent non-necrotizing granulomatous inflammation, closely mimicking sarcoidosis and resulting in diagnostic delay. The granulomas were large and well-formed, unlike the smaller epithelioid histiocytes typically described in the lymphohistiocytic (Lennert) variant of PTCL, which likely contributed to the initial interpretation as a non-neoplastic granulomatous process. Infectious etiologies were excluded, and coexisting sarcoidosis was clinically ruled out based on the acute presentation with bulky disseminated lymphadenopathy, elevated LDH, and absence of cardiac or other extranodal involvement.

Importantly, this case reinforces the association between a prominent inflammatory or histiocytic background and a **TH1-associated transcriptional program** in PTCL-NOS. After excluding a TFH phenotype, the lymphoma was classified as the PTCL-TBX21 biologic subtype using a validated IHC-based algorithm, supported by strong CXCR3 expression (31562134). Consistent with prior studies, PTCL-NOS cases with inflammatory or granulomatous backgrounds preferentially align with a TBX21-driven biology, indicating that the inflammatory milieu is biologically linked to tumor subtype rather than incidental (31562134, 39491745).

Overall, this case raises the possibility that inflammatory microenvironmental features in PTCL-NOS may be biologically driven.

Panel Diagnosis: PTCL-NOS with granulomata, TBX21 subtype

EA4HP26-LYWS-358

ALK-negative anaplastic large cell lymphoma with atypical morphology (small cell variant)

Dr. Kylie Everard, **Dr. Ali Sakhdari**

University Health Network, University of Toronto, Laboratory Medicine and Pathobiology, Toronto, Canada

Case Description

- Previously healthy 69-year-old male.
- Presented with lymphadenopathy and generalized weakness.
- CT abdomen/pelvis revealed a heterogeneously enhancing right inguinal mass with central hypoattenuation measuring 5.9 x 5.1 x 4.6 cm, with adjacent enlarged right inguinal and right iliac chain lymph nodes, measuring up to 3.2 cm in maximum dimension.
- Core biopsy was performed on the right inguinal lymph node.

Biopsy Fixation Details

- The majority of specimens were submitted in 10% buffered formalin.
- A small portion of the specimen received in RPMI and submitted for flow cytometry.

Frozen Tissue Available

- No frozen tissue was available for this case.

Details of Microscopic Findings

- Morphology demonstrates nodal architecture, which is effaced by sheets of predominantly small to intermediate-sized, atypical lymphocytes with rare large cells. Prominent pleomorphism is not identified.
- Rare, large anaplastic appearing (Hullmark) cells are present.
- Lesional cells demonstrate clear to eosinophilic cytoplasm, with some demonstrating prominent nucleoli.
- Occasional small, unremarkable lymphocytes and rare plasma cells are identified in the background.

Immunophenotype

- By immunohistochemistry:
POSITIVE: CD30 (strong and diffuse [100%], CD2, CD3(dim), CD45, BCL2(weak), MUM-1, p63

- **NEGATIVE:** ALK, CD4, CD5, CD7, CD8, BCL6, CD10, CD34, PAX5, TdT, CD20, CD138, Cyclin D1, EBER ISH, CD117, SOX10, AE1/AE3, and D2-40.
- p53 is expressed in the majority of neoplastic cells.
- Ki67 proliferative index is >90%.
- Flow cytometry was non-contributory, as the specimen consisted mainly of necrotic debris and was insufficient for analysis.

Cytogenetics

- FISH studies for DUSP22 and TP63 gene rearrangements have been ordered, and results are pending.

Molecular Studies

- NGS lymphoma panel has been ordered and results are pending.

Proposed Diagnosis

- ALK-negative anaplastic large cell lymphoma, small cell variant

Interesting Feature(s)

Classic ALK-negative ALCL morphology is typically pleomorphic, with sheets of large atypical lymphoid cells, including multinucleated “hallmark” cells.

This case exhibits a prototypical ALK-negative ALCL immunophenotype, characterized by diffuse CD30 expression, but lacks significant pleomorphism. The neoplastic population is composed predominantly of small to intermediate-sized, relatively monomorphic cells, with only rare scattered larger anaplastic/hallmark cells. p63 expression raises the possibility of an underlying TP63 gene rearrangement, a known abnormality in a subset of ALK-negative ALCL.

Overall, we favour classifying this neoplasm as a small-cell variant of ALK-negative ALCL, rather than PTCL, NOS, given the combination of diffuse CD30, supportive ancillary findings (including p63), and the recognition that anaplastic morphology may be focal or inconspicuous in some ALK-negative ALCL cases.

More broadly, this case supports the concept that ALK-negative ALCL should be defined primarily by immunophenotypic and molecular features, and that morphologic subtyping (analogous to the variant patterns recognized in ALK-positive ALCL) may be appropriate in selected ALK-negative ALCL cases.

Panel Diagnosis: PTCL-NOS expressing CD30

EA4HP26-LYWS-360

ALK-negative anaplastic large cell lymphoma, *TP63*-rearranged with leukemic presentation and hemophagocytic lymphohistiocytosis

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Case Description

A 53-year-old woman presented (11/2020) with progressive cervical lymphadenopathy and abdominal/back pain. PET-CT showed multifocal FDG-avid adenopathy above and below the diaphragm (SUVmax 16.9) with splenic uptake (SUVmax 7.0). Initial blood counts demonstrated leukocytosis with circulating atypical cells; cervical lymph node biopsy was performed for diagnosis.

The patient received brentuximab-based multi-agent chemotherapy with initial metabolic response, followed by allogeneic peripheral blood stem cell transplantation (PBSCT) in 03/2021. She experienced early relapse with disseminated involvement of nodal sites, bone marrow, peripheral blood and CSF and progressive refractoriness. Bone marrow biopsy at relapse demonstrated low-level lymphoma involvement (~5–10%) with prominent histiocytic

activation and hemophagocytosis. The terminal course was characterized by refractory CMV viremia, hemophagocytic lymphohistiocytosis and tumor lysis syndrome.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

Diffuse effacement by a pleomorphic large cell lymphoma composed of intermediate-to-large atypical cells with irregular folded nuclei, conspicuous nucleoli, and abundant cytoplasm, including “popcorn” forms. Brisk mitotic activity and apoptosis were present; residual follicular structures were largely absent.

Immunophenotype

Neoplastic cells:

Express: CD2, CD8, CD30 strong/diffuse, p63, cytotoxic markers, CD56; Ki-67 ~90%.

Do not express: CD3 (surface and cytoplasmic), ALK, CD4, CD5, TCR β , TCR δ .

Tissue flow cytometry: dominant abnormal population (~88% of WBCs) CD2+, CD56+, CD30+, CD8(partial) with absent s/cCD3 (NK-like/null).

Peripheral blood flow cytometry showed a similar abnormal population comprising ~72% of WBCs at presentation.

Cytogenetics

FISH using TP63 break-apart probe detected TP63 (3q28) rearrangement (~32% of nuclei at diagnosis).

Molecular Studies

At diagnosis:Archer FusionPlex anchored multiplex PCR identified an in-frame *TBL1XR1*(ex7)–*TP63*(ex4) fusion. Targeted NGS/CNV showed homozygous *CDKN2A/CDKN2B* (9p21) deletion and *GATA3* loss, with missense variants in *CDK8*, *KMT2D*, and *SGK1* (VAF ~20–30%). The CNV profile suggested additional broad arm-level imbalances (e.g., 17q and 21q gains; 16q loss; 17p13 region including TP53; 19p13; X). TCR gene rearrangement studies (β/γ) were negative, consistent with a null/NK-like phenotype.

At relapse: NGS on flow-sorted tumor cells confirmed *TP63-TBL1XR1* fusion and showed increased CNV burden with a complex 19p13 CNV cluster.

Proposed Diagnosis

ALK-negative anaplastic large cell lymphoma (ALCL), *TP63*-rearranged

Lymph nodes and bone marrow involved at presentation with peripheral blood atypical cell population of 72%.

Interesting Feature(s)

TP63-rearranged ALK-negative ALCL presenting with a rare leukemic phase and fulminant refractory course despite intensive therapy and allo-PBSCT. Persistence of founder lesions (*TP63-TBL1XR1* fusion; *CDKN2A/B* loss; *KMT2D/SGK1* variants) supports clonal continuity. LA-HLH likely reflected convergence of high tumor burden, lymphoma-driven cytokine signaling, therapy-related immune dysfunction, and inflammatory triggers (e.g., CMV/tumor lysis).

Panel Diagnosis: ALK- ALCL in leukemic phase (*TP63* rearranged) and HLH (during progression)

EA4HP26-LYWS-380

Peripheral T cell lymphoma, not otherwise specified, lymphoepithelial (Lennert) variant

Prof. Shaoying Li, Dr. Lianqun Qiu, Dr. Jie Xu

UT MD Anderson Cancer Center, Hematopathology, Houston, USA

Case Description

The patient is a 59 yo female with a history of peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), lymphoepithelial (Lennert) variant, diagnosed at outside from a left axillary lymph node biopsy 2 years ago. She received CHOPx3, then CEOPx3 with refractory disease and then auto-SCT and reached remission. Recent PETCT showed interval increase in size and metabolic activity of left axillary nodes.

Biopsy Fixation Details

Left axillary node biopsy was fixed in 10% neutral buffered formalin (NBF).

Frozen Tissue Available

NA

Details of Microscopic Findings

Histologic sections reveal nodal tissue partially infiltrated by small to medium sized atypical lymphocytes with irregular nuclei and somewhat open chromatin. Scattered larger cells are seen. Many scattered or clustered epithelioid histiocytes are seen. Residual lymphoid follicles are noted in the background.

Immunophenotype

Immunohistochemistry studies showed: The lymphoma cells are positive for CD3, CD4, CD5, TIA1, Granzyme B (subset) and negative for CD7, CD8, BCL6, BCL2, PD1, CXCL13, ALK1, TCL1, and TDT. CD20 and PAX5 highlight B cells, mainly in background residual follicles with associated CD21+ follicular dendritic meshworks. Proliferation index by Ki67 is 5-10% in the lymphoma cells.

EBER by in situ hybridization is negative.

AFB and GMS special stains are negative for acid-fast bacilli and fungal microorganisms, respectively.

Flow cytometry shows aberrant T cells which are positive for CD45, CD4 (decreased), CD26, CD5 (decreased), CD2, TCR A/B (decreased), CD25 (partial), CD52, and negative for surface CD3, CD7, CD8, CD10, CD16, CD30, CD56, CD57, CD94, TCR G/D. The lymphoma cells are monotypic by TRBC1 negativity.

Cytogenetics

NA

Molecular Studies

NA

Proposed Diagnosis

Peripheral T cell lymphoma, not otherwise specified, lymphoepithelial (Lennert) variant

Interesting Feature(s)

§Lennert lymphoma is characterized by numerous epithelioid histiocytes or granulomatous inflammation, which can mask the lymphoma and leading to misdiagnosis

§The lymphoma cells in this case are surface CD3 negative with total loss of CD7. Despite the CD4 expression, the lymphoma cells express cytotoxic markers TIA1 and Granzyme B.

§Although previous literature suggest Lennert lymphoma has a better prognosis compared to PTCL, NOS, this patient relapsed 2 years after chemotherapy and auto-SCT.

Panel Diagnosis: PTCL-NOS lymphoepithelioid variant (Lennert lymphoma)

2-year-old boy with ALK+ ALCL and secondary hemophagocytic lymphohistiocytosis

PhD/MD Ashley Eckel^{1,2}, Dr. Sandra Bohling^{1,2}, PhD/MD Jonathan Fromm², PhD/MD Karen Chisholm^{1,2}

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Case Description

A 2 year-old boy presented with fevers, maculopapular rash on face and chest, and periorbital edema. He was found to have an oral lesion positive for VZV (postulated to be vaccine reactivation). EBV testing showed positive IgM and IgG and EBV PCR 398 IU/mL. Ultrasound identified several enlarged lymph nodes in the neck, one of which was biopsied. The patient was diagnosed with anaplastic large cell lymphoma (ALCL), ALK positive. Bone marrow showed rare ALK+ cells and plentiful hemophagocytic histiocytes. CSF was negative. Laboratory studies demonstrated bilineage cytopenias (platelets 59 K/uL, hemoglobin 8.9 g/dL, ANC 1591 K/uL), with elevated triglycerides (301 mg/dL), ferritin (1,100 ng/mL), LDH (4,066 IU/L), and sIL2R (56,743 units/mL). The patient was diagnosed with secondary malignancy-associated hemophagocytic histiocytosis (HLH). Therapy included dexamethasone, cyclophosphamide, cytarabine, methotrexate, ifosfamide, etoposide, hydrocortisone, doxorubicin, and intrathecal methotrexate, leading to CR. Less than 2 months after the end of therapy, he presented with fever and seizures, and was found to have relapsed ALK+ ALCL with nodal, CNS, and marrow involvement, as well as reactivated HLH (sIL2R 20,182 units/mL). He received intrathecal triple therapy, dexamethasone, brentuximab, and lorlatinib, and bone marrow transplant. He is currently more than six years without recurrence.

Biopsy Fixation Details

Formalin-fixed, paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

H&E-stained slides showed sections of lymph node with diffuse infiltration by large atypical cells, numerous histiocytes, and mature lymphocytes. The large atypical cells included multinucleate forms with irregular nuclei, stippled chromatin, and inconspicuous nucleoli. Mitotic figures were frequent. Hemophagocytosis was noted in a subset of the histiocytes. Bone marrow evaluation identified a mildly hypercellular marrow with rare scattered CD30+ALK+ cells and numerous hemophagocytic histiocytes. At relapse, diagnosis was predominantly made via imaging, but CSF cytology identified medium-to-large sized cells with multiple nucleoli and deeper basophilic cytoplasm, with a perinuclear halo and eosinophilic granules. Bone marrow showed rare (<1%) neoplastic cells.

Immunophenotype

At diagnosis, the neoplastic cells were positive for CD3, CD30, and ALK1, and negative for CD20. CD163 stain highlighted histiocytes. Scattered EBV positive cells were present. At relapse, CNS flow cytometry showed neoplastic cells expressing CD4 (dim), CD8, CD2 (variable), CD3 (minor subset), CD7 (bright), CD30, CD38, and CD45, and bone marrow flow cytometry identified 0.4% neoplastic cells.

Cytogenetics

Normal male karyotype 46,XY[20] (bone marrow).

Molecular Studies

A germline assay was negative for mutations of immunodeficiency genes.

Proposed Diagnosis

ALK-positive anaplastic large cell lymphoma (ALCL)

Interesting Feature(s)

Pediatric ALCL often presents with advanced stage disease, extranodal involvement, and systemic symptoms. Secondary HLH has been reported in association with ALCL in approximately 10% of cases. Cases of ALCL with

associated HLH more frequently showed CNS and bone marrow involvement; however, some reports suggest the degree of marrow involvement by lymphomas associated with HLH can be subtle. In this submitted case, the patient showed advanced stage disease with subtle marrow involvement at presentation. Additional CNS involvement was seen at relapse. While HLH is a potentially life-threatening condition characterized by hyperinflammation, outcomes in ALCL patients with and without lymphoma associated HLH are similar.

Panel Diagnosis: ALK+ ALCL with HLH

EA4HP26-LYWS-391

Challenging diagnosis of a nodal T follicular helper cell lymphoma NOS, with epithelioid granulomata and cytotoxic T-cell expansion

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Case Description

A 43-year-old man with no significant past medical history presented with disseminated lymphadenopathy showing increased metabolic activity (SUVmax 19). The infectious workup was negative. An excisional biopsy of an inguinal lymph node was performed.

Biopsy Fixation Details

Buffered formalin

Frozen Tissue Available

NO

Details of Microscopic Findings

Histologic analysis showed an almost complete effacement of the nodal architecture with massive expansion of interfollicular areas and vascular hyperplasia. High-power examination revealed a non-necrotizing epithelioid granulomatous reaction, small- to medium-sized slightly atypical lymphocytes, admixed with eosinophils, plasma cells and rare larger lymphoid elements.

Immunophenotype

Atypical T-cells were CD3+, CD5+, CD2+, CD7-, TCRα+, TRBC1-, CD4+, outnumbered by activated cytotoxic CD8+ T-cells. The atypical T-cells were CD10+, PD1+, ICOS+, some of them BCL6+ and CXCL13+, occasionally CD30+, and formed small clusters. Scattered large cells were PAX5+, showed heterogenous expression of CD20 and CD30, were EBER+ and EBNA2-. No expansion of the FDC meshwork was seen (CD21/CD23).

Cytogenetics

NA

Molecular Studies

TCR gene rearrangement analysis demonstrated a dominant monoclonal T-cell population. Targeted-NGS 15-gene panel dedicated to T-cell lymphomas identified two *TET2* variants (p.R979fs, VAF 11.9% ; p.Q1553fs, VAF 8.4%). No *RHOA* mutation was identified.

Proposed Diagnosis

Nodal T follicular helper cell lymphoma (nTFHL) NOS, with epithelioid granulomata and expansion of cytotoxic T-cells.

Interesting Feature(s)

- nTFHL are frequently associated with a prominent and potentially misleading inflammatory background. When accompanied by epithelioid granulomatous reaction and expansion of cytotoxic CD8+ T-cells, the histologic

appearance may mimic peripheral T-cell lymphoma, NOS, lymphohistiocytic variant. However, open cortical sinus, arborizing vessels and expansive follicular dendritic cell (FDC) meshwork (CD21/CD23/CD35) within T-cell areas should raise suspicion for nTFHL.

- nTFHL typically show a T-cell infiltrate with frequent loss of CD7 (~50%) while other pan-T-cell markers are usually preserved. Mixed CD4/CD8 populations are common and cytotoxic activated CD8+ T cells may be predominant. TRBC1 loss or overexpression in atypical T-cells (sCD3+) supports clonality but may be challenging to interpret. Diagnosis requires expression of at least 2-3 TFH markers ; CD10 and CXCL13 are the most specific but less sensitive, whereas PD1 and ICOS are more sensitive but less specific. Usually, heterogenous CD30 expression may be observed in a subset of neoplastic TFH cells, as in our case.

- Clonal TCR gene rearrangement is supportive but not diagnostic and may be absent. Molecular findings confirm the diagnosis when *RHOA* p.G17V mutation (40–70%) is identified. Mutations involving *TET2* (50-80%) and/or *DNMT3A* (20-40%) can be related to clonal hematopoiesis. Therefore, they are not specific but highly suggestive, when integrated with typical morphologic and immunophenotypic features. In our case, the presence of two *TET2* variants with a VAF consistent with the neoplastic T-cell content in a young patient in the clinico-pathological context may have some diagnostic value.

Panel Diagnosis: nTFHL /TFHL-NOS with granulomata and cytotoxic T-cell expansion

EA4HP26-LYWS-394

An atypical case of primary peripheral T cell lymphoma – NOS in a young patient presenting a genetic immunodeficiency.

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Case Description

A 36 year-old-man with a history of congenital anosmia, hypogonadism, profound lymphopenia, class-switched memory B-cell deficiency, severe hypogammaglobulinemia (4.4 g/L) and a germline mutation in *SEMA3E* presented with axillary and inguinal polyadenopathy, diffuse pain, but no B symptoms. HTLV1 serology was negative and LDH was elevated (360 UI/L). A biopsy of the right axillary node was performed.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

The two core needle biopsy specimens show a lymph node with effaced architecture replaced by a diffuse lymphoid proliferation composed of small lymphocytes with round nuclei, mild cytologic atypia, and dense chromatin. The neoplastic lymphocytes are distributed within a histiocyte-rich background, with rare reactive lymphocytes and scattered eosinophils.

Immunophenotype

The atypical lymphoid cells are: CD2+, TIA+, Perforine+, Granzyme+, CD3-/+ (partial expression), CD5-, CD7-, CD4-, CD8-, TRBC1- (null phenotype), CD30-, CD10-, CD23-, CD34-, TdT-, TCL1-, ALK1-, TCR delta-, TCR B F1-, CD20-, PAX5-, GATA3-, CD56-, p53- (wildtype), STAT3-, CD1A-, MUM1-, INI1+(retained expression). EBV-encoded RNA (EBER) in situ hybridization is negative on atypical cells. Ki-67 proliferation index is 70%.

Cytogenetics

NA

Molecular Studies

Clonality analysis : Monoclonal TCR rearrangement.

Whole exome sequencing: presence of pathogenic mutations in the following genes: *TNFRSF14*, *JAK1*, *JAK3*, *DDX3X*, *SMARCA4*, *KIT* and *PABPC1*.

Copy-number analysis showed amplifications involving 1q (MCL1, SETDB1, BCL9, AKT3), 2p (MYCN, REL, BCL11A, XPO1), and 2q33 (CD28), consistent with activation of survival (PI3K/AKT, NF-κB), TCR co-stimulation (CD28), and proliferative pathways. Recurrent losses affected 1p (TNFRSF14, SKI), 3p (BAP1, RHOA), 4q (FAT4, IL2), 6q (ARID1B, LATS1), and 15q (B2M), involving tumor suppressor and epigenetic regulator genes. These changes resulted in biallelic TNFRSF14 inactivation (mutation plus deletion).

RNA-sequencing : presence of a VAV1::THAP4 translocation.

Proposed Diagnosis

Cytotoxic peripheral T cell lymphoma not otherwise specified with cytotoxic phenotyp, in a context of genetic immunodeficiency, with the presence of a VAV1 fusion.

Interesting Feature(s)

- presence of a peripheral T cell lymphoma not otherwise specified with cytotoxic profile in a young patient with an associated genetic immunodeficiency (Nicolae et al.).
- unusual morphology with small inconspicuous, discretely atypical tumoral cells disposed in a background rich in histiocytes and scattered eosinophils – Lennert-like.
- presence of an almost T cell null immunohistochemical profile (CD2+, CD3-, CD5-, CD7-, CD4-, CD8-) of lymphoid cells with the strong expression of cytotoxic markers.
- an unusual molecular profile showing JAK/STAT activation (JAK1/JAK3), enhanced TCR signaling (CD28 gain, VAV1::THAP4) and immune evasion (biallelic TNFRSF14 alterations) which is in concordance with the findings described by Nicolae et al.
- presence of VAV1::THAP4 translocation which is described in PTCL-NOS and is associated with an activation of VAV1. (Abate F et al)

Panel Diagnosis: cytotoxic PTCL-NOS associated with genetic immunodeficiency

EA4HP26-LYWS-395

T cell lymphoma with indolent clinical behaviour and variable, evolving histological features across consecutive biopsies.

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Case Description

39 year old woman presented in 2020 with cervical lymphadenopathy and hearing loss. No B symptoms. PET scan 2021: Soft tissue in the posterior nasopharynx 2 x 5.5 cm. Mild FDG uptake in small volume bilateral cervical and supraclavicular nodes, up to 20 mm short axis (SUVmax 6). Followed up from 2020 to present. Initially treated with CHOP (mid to late 2021); good response to cycle 1 but progression after cycle 3. No response to methotrexate. Commenced on cyclosporin in early 2022 in view of the indolent clinical course of disease. Imaging shows slowly progressive disease. The patient remains well on cyclosporin.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph nodes 1&3: Paracortical expansion and high endothelial venule proliferation, small lymphocytes showing minimal atypia admixed with variable numbers of eosinophils, microgranulomata and plasma cells. Inconspicuous mitoses and apoptosis.

Post nasal biopsy: similar features as above but with partial architectural effacement.

Lymph node 2(PET +): histologically normal.

Lymph node 4(submitted): Similar to lymph nodes 1 and 3 + scattered large anaplastic cells appear.

Lymph node 5: Architectural effacement by a diffuse polymorphic infiltrate comprising of abundant eosinophils, histiocytes forming microgranulomata and clearly atypical variably sized lymphocytes. Large anaplastic cells are absent.

Immunophenotype

Lymph nodes 1 & 3 (2021; previously submitted EAHP/SH 2023):

T cells :No antigen loss, CD4:CD8 ratio of ~3:1. PD1, CD10, BCL6, and Granzyme B were negative. Ki67 10–20%, EBER ISH-.

Lymph node 4 (August 2025; submitted EAHP 2026):

Background as above. Plus large anaplastic cells, CD30+, CD2+, CD15+, with weak MUM1 expression and strong p53 positivity, Ki67+. Negative for B-cell markers and TFH markers (CD10, BCL6, PD1, ICOS, CXCL13), cytotoxic markers, ALK1 & EBER ISH.

Lymph node 5 (December 2025):

CD2+ and CD4+, CD3, CD5, CD7, CD8-. PD1, ICOS, CXCL13, and EBER ISH-. Ki67~40%. Scant small CD30+ cells.

Cytogenetics

NA

Molecular Studies

Euroclonality NDC

Structural variants TRAJ::BCL3 / t(14;19) VAF 10%

Sequence variants TNFAIP3 NM_001270508.2 c.786_791delinsAG p.(Leu263GlyfsTer23) VAF 4%

Clonal TCR gene rearrangements:

TRA TRAV24/TRAJ33

TRB TRBD1/TRBJ2-7, TRBD2/TRBJ2-1, TRBV9/TRBJ1-1

TRG TRGV3/TRGJ2, TRGV4/TRGJ2

Proposed Diagnosis

Indolent T cell lymphoproliferative disorder unclassified

Interesting Feature(s)

Indolent T-cell lymphoma with sustained low-grade clinical behaviour over a five-year period (2020–2025). Three lymph node biopsies in 2021 demonstrated a Lennert's lymphoma-like background with clonal T-cell receptor (TCR) gene rearrangement studies. In August 2025, a lymph node biopsy showed the emergence of scattered large anaplastic T cells expressing CD2, CD15, and CD30(submitted case). This may conceivably be classified as ALK-negative anaplastic large cell lymphoma (ALCL), potentially of lymphohistiocytic type. Notably, while this variant is recognised in the WHO and ICC classifications for ALK-positive ALCL, it is not formally described in ALK-negative ALCL EuroClonality NDC identified a low-level TNFAIP3 sequence variant and an unusual TRA::BCL3 translocation. A subsequent biopsy in December 2025 demonstrated clonal evolution, with an increased proliferative index and partial T-cell antigen loss. Importantly, the large anaplastic cells observed in the August 2025 biopsy were not identified in any other specimen. The patient remains clinically well on cyclosporin 200mg at last follow up in January 2026.

Panel Diagnosis: PTCL-NOS, cytotoxic

Lennert Lymphoma: A Rare Variant of Peripheral T-Cell Lymphoma with a Unique Tumor Microenvironment

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Case Description

A 63-year-old female presented with fatigue, bilateral thigh numbness, and generalized lymphadenopathy. Initial MRI workup revealed pelvic and retroperitoneal adenopathy. PET scan confirmed widespread FDG-avid lymph nodes in the neck, thorax, abdomen, pelvis, and bilateral inguinal regions, along with splenomegaly, suspicious for lymphoma. An excision of the right axillary lymph node was performed for diagnosis.

Biopsy Fixation Details

Tissue was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

None

Details of Microscopic Findings

The excised lymph node showed effaced nodal architecture by an atypical lymphoid proliferation and numerous non-necrotizing granulomas composed of epithelioid histiocytes. The lymphoid proliferation comprises predominantly small to medium-sized lymphoid cells, some with mild atypia characterized by slightly larger size and more open chromatin, scattered large atypical lymphoid cells, and occasional eosinophils. Few residual follicles were present peripherally. No definitive microorganisms were found on special stains.

Immunophenotype

- **IHC:** Atypical T cells were positive for CD2, CD3 (dim), BCL2, and negative for CD5, CD7, CD8, PD1, CD10, MUM1, CD30, TIA-1, granzyme B, ALK1 and EBER. CD4 expression was difficult to determine. GATA3 highlighted many T-cells. The epithelioid histiocytes of the granulomas were positive for CD68, CD4 but negative for CD163. The Ki-67 proliferation index was ~20% and appeared positive in the majority of atypical cells. CD20 and PAX5 highlighted residual B cell follicles. Cytokeratin AE1.3 was negative.
- **Flow Cytometry:** Aberrant T-cell population (7% of lymphocytes) was identified in a background of normal reactive T lymphocytes (65% of lymphocytes). The abnormal T-cells were positive for bright CD2, dimCD3, TCRαβ, TRBC1, and negative for CD4, CD5, CD7, CD8, CD30, CD25, TCRγδ, CD10 and CD279.

Cytogenetics

Abnormal complex karyotype - 46,XX,add(1)(p32),dup(1)(q21q32),+3,add(3)(p13),del(3)(q12q25),-4,+5,+6,add(6)(p21),add(8)(p11.2),+9,add(9)(q13),i(9)(q10),-10,add(11)(q23),-13,14,der(19)del(19)(p13)t(14;19)(q11.2;q13),+3mar[cp10]/46,XX[10].

Molecular Studies

- **IGH and IGK gene rearrangement:** Negative.
- **TCR-gamma gene rearrangement:** Positive (clonal in a polyclonal background).
- **NeoTYPE® Analysis** (Next-Generation Sequencing): No pathogenic mutations detected.

Proposed Diagnosis

Peripheral T-cell lymphoma, lymphoepithelioid variant (Lennert lymphoma)

Interesting Feature(s)

This case illustrates Lennert lymphoma, a rare subtype of peripheral T-cell lymphoma, which is often challenging to diagnose and distinguish from reactive granulomatous lymphadenopathy. It demonstrates the utility of flow cytometry in identifying the neoplastic T-cell population, which is often present in small numbers and is masked by reactive T-cells. In our case, the neoplastic T cells are double-negative (CD4-CD8-) in contrast to typical CD4+ (in most cases) or CD8+ phenotypes. CD163 is usually expressed in M2 macrophages. In our case, the absence of CD163 from the

epithelioid histiocytes in the granulomas indicated an M1 (classically activated/pro-inflammatory) macrophages. In addition, GATA3 highlights many T-cells. These findings provide evidence for a distinct tumor microenvironment characterized by M1 macrophages and Th2 cells in Lennert lymphoma.

Panel Diagnosis: PTCL-NOS with granulomatous response, prominent but falling short of 'Lennert lymphoma'

EA4HP26-LYWS-408

ALK1-negative anaplastic T-cell lymphoma with secondary hemophagocytic lymphohistiocytosis

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Case Description

A 71 year old male sought medical care due to weight loss and night sweats and a lymph node conglomerate in the left groin was noted upon examination. TARC levels were increased. A diagnosis of lymphoma was made and treatment with BV-CHEPx5 and subsequently Gemcitabin-Oxaliplatin was initiated. During Gemcitabin-Oxaplatin treatment the patient developed pancytopenia, increased ferritin (2,500 ug/L), fever and splenomegaly.

Biopsy Fixation Details

Fine needle aspirates and core needle biopsies from the lymph node conglomerate, as well as peripheral blood smears, bone marrow smears and bone marrow biopsies were investigated. The bone marrow biopsies and lymph node tissue were fixated in 4% formalin and thereafter the bone marrow biopsies were decalcified using an EDTA protocol.

Frozen Tissue Available

No

Details of Microscopic Findings

Initially, the findings of the fine needle aspirates and core needle biopsies of the lymph node material could only establish a diagnosis of a CD30-expressing malignant tumor of unknown etiology due to the sparseness of tumor cells and a florid inflammatory background including histiocytes, eosinophils and lymphoplasmacytic infiltrates. Additional biopsies were taken where morphologically areas of large, atypical cells including variants with "horse-shoe" shaped and peripherally located nuclei, were noted. Intersecting fibrosis and a mixed inflammatory infiltrate as described in the former biopsies were seen. In bone marrow smears an increase of hemophagocytes were noted.

Immunophenotype

Immunohistochemical stainings of the lymph node showed positive staining in the atypical cells for CD30, CD25, CD43, CD4, MUM1 and cytotoxic markers (TIA1, GranzymeB) and possibly a weak, partial staining of CD2. Other T- and B-cell markers such as CD3, CD5, CD7, CD8, CD79A, CD20 and PAX5 were negative

Cytogenetics

Not performed.

Molecular Studies

Molecular studies by PCR regarding rearrangements of the B- and T-cell receptors were performed on the initial sample and a small, isolated rearrangement of IgK was seen. Rearrangement of TCR could not be assessed due to low amplification.

Proposed Diagnosis

Anaplastic T-cell lymphoma (ALCL), ALK1-negative, and secondary hemophagocytic lymphohistiocytosis (HLH).

Interesting Feature(s)

Interesting features includes the correlation of ALCL with secondary HLH, which is rare especially in adults. Elevated TARC-levels which has to a large extent been shown to be correlated with classical Hodgkin disease.

However, some anaplastic T-cell lymphomas do demonstrate increased levels of TARC, especially in ALK1-negative cases.

Also, it highlights the difficulties in the initial diagnosis of ALCL in material with a florid inflammatory background and no demonstrable TCR rearrangement.

Panel Diagnosis: ALK- ALCL and HLH

EA4HP26-LYWS-416

Peripheral T-Cell Lymphoma (PTCL-NOS) with a Lennert-like Pattern in patient diagnosed with sarcoidosis

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Case Description

An 18-year-old female with a history of *TNNI3*-mutated restrictive cardiomyopathy (s/p orthotopic heart transplant 15 years prior) and pulmonary sarcoidosis (diagnosed 11 years prior, currently off steroids) presented with refractory vomiting, diarrhea, and weight loss (>10 lb). Initial endoscopic biopsies (EGD and colonoscopy) were negative for PTLN and interpreted as compatible with celiac disease; however, subsequent serology was negative for celiac antibodies. Due to persistent abdominal pain and clinical decline, a CT scan was performed two months later, revealing abdominal and right inguinal lymphadenopathy. The patient was admitted for a core needle biopsy of the inguinal node.

Biopsy Fixation Details

The right iliac lymph node core biopsy tissue was fixed in formalin.

Frozen Tissue Available

None available.

Details of Microscopic Findings

H&E. sections of the right iliac lymph node core biopsy revealed granulomatous inflammation with numerous epithelioid granulomas interspersed with mildly atypical mostly medium-sized lymphocytes admixed with occasional histiocytes.

Immunophenotype

- **Flow cytometry immunophenotyping** identified an abnormal T-cell population (approximately 60% of viable cells) expressing CD45, positive for CD2 (brighter than normal), cytoplasmic CD3 (brighter than normal), CD5 (dimmer than normal), CD7. The cells were negative for surface CD3, CD8, CD10, CD19, CD20, CD34, CD99, CD1a and TdT.
- **Immunohistochemistry (IHC)** revealed that the atypical cells were positive for CD2, CD3, CD4, and TCR beta-F1, while negative CD8, CD10, TIA-1, BCL6, CD25, CD30, CD34, CD56, PD-1, ICOS, TdT, ALK, and TCR-delta, TCR-delta. Scattered B cells were highlighted by CD20 and PAX5. EBER-ISH for EBV was negative.

Cytogenetics

Not performed.

Molecular Studies

- **PCR:** Tcell receptor (gamma) gene rearrangement analysis was positive, identifying a monoclonal T-cell population.
- **Nextgeneration sequencing (NGS):** Comprehensive analysis (including RNA, DNA, and copy number variants) performed on the lymph node biopsy detected a pathogenic variant in the *TET2* gene. No clinically significant copy number variants were identified.

- o Tier II: Variants of Strong Clinical Significance: *TET2* NM_001127208.2 p.His850Tyrfs*4 (c.2544_2547dup) AF: 18.3%
- o Tier III: Variants of Unknown Clinical Significance: *KIT* NM_000222.2 p.Ile563Lys (c.1688T>A) AF: 47.8%

Proposed Diagnosis

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), consistent with monomorphic post-transplant lymphoproliferative disorder (PTLD) of T-cell type.

Interesting Feature(s)

- Clinical and Diagnostic Pitfall: This case highlights a deceptive clinical presentation—initially misdiagnosed as celiac disease—where the morphology mimicked benign granulomatous inflammation in a patient with a history of sarcoidosis. This significant overlap necessitates a comprehensive integration of clinical, morphological, and molecular data to accurately differentiate sarcoid-like features from an underlying lymphoma.
- Late-Onset PTLD: T-cell PTLD is an exceedingly infrequent diagnosis and remains poorly characterized. Unlike B-cell PTLD, T-cell variants in immunodeficient settings are frequently EBV-negative, as demonstrated in this late-onset case.
- Molecular Significance: This case identified a loss-of-function mutation in *TET2*, a key regulator of DNA methylation. While *TET2* alterations are documented in PTCL, NOS (especially those with a follicular helper T-cell lymphoma), their specific prevalence and pathogenic role in the PTLD setting remain largely undefined.

Panel Diagnosis: PTCL-NOS, EBV- in the setting of ID

EA4HP26-LYWS-429

ALK-Negative Anaplastic Large Cell Lymphoma

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Case Description

A 64-year-old man with COPD and alcohol use disorder presented with rapidly progressive lymphadenopathy and B symptoms concerning for high-grade lymphoma. He reported fevers to 39°C, drenching night sweats, unintentional 14-kg weight loss over 4 months, and progressive inguinal and submandibular lymphadenopathy.

Initial investigations showed hypercalcemia (3.41 mmol/L), elevated lactate (3.3 mmol/L), acute kidney injury, hyperuricemia (693 µmol/L), LDH >2,500 U/L, ferritin >8,000 µg/L, triglycerides 5.4 mmol/L, and marked cholestatic liver injury. Soluble IL-2 receptor was elevated at 15,135 U/mL. Examination revealed extensive cervical, submandibular, and inguinal lymphadenopathy.

CT imaging demonstrated bulky inguinal, axillary, mediastinal, and hilar lymphadenopathy with heterogeneous bone marrow. Excisional lymph node and bone marrow biopsies confirmed ALK-negative anaplastic large cell lymphoma (CD3-/CD20-/CD30+), with a DUSP22 rearrangement in 75% of nuclei and no TP63 rearrangement. PET imaging revealed widespread FDG-avid nodal and extranodal disease. He was initiated on cyclophosphamide, doxorubicin, prednisone, and brentuximab vedotin on PAD10 and has completed two cycles at the time of submission.

Biopsy Fixation Details

B+ fixative for a minimum of 3 hours and then 1hr into decal solution. Rinsed with water for 15 min and then placed into formalin fix for ~7 hrs until the processing.

Frozen Tissue Available

Frozen tissue is not available.

Details of Microscopic Findings

Left supraclavicular lymph node:

Microscopic examination revealed effacement of the nodal architecture by a diffuse proliferation of large, atypical lymphocytes.

Bone marrow biopsy: Sections show an extensive atypical lymphoid infiltrate in a diffuse, sheet-like pattern. The atypical lymphocytes are large and pleomorphic, with irregular lobulated nuclear contours, prominent nucleoli, and a moderate amount of amphophilic cytoplasm. Frequent mitotic figures and “hallmark” cells with horseshoe-shaped nuclei are identified.

Immunophenotype

Flow cytometry (10-color lymphoma screening panel) on the lymph node specimen detected an atypical population of CD45-positive cells (red events) with high forward scatter (not shown) and intermediate side scatter, expressing CD2 but lacking surface CD3.

Cytogenetics

Result: Positive for a DUSP22 rearrangement.

ISCN: nuc ish (DUSP22)x2(5'DUSP22 sep 3'DUSP22)x1[150/200]

Result: Negative for a TP63 rearrangement.

ISCN: nuc ish (TP63)x2[200]

Molecular Studies

Positive for a DUSP22 rearrangement.

Proposed Diagnosis

ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA

Interesting Feature(s)

Circulating tumor cells: Presence of circulating ALCL/hallmark cells, which is uncommon but concordant with the extensive bone marrow involvement observed.

Immunophenotypic profile: The immunoprofile is highly characteristic of a DUSP22-rearranged (DUSP22-R) phenotype in ALK-negative ALCL.

Key diagnostic markers: In ALK-negative ALCL, CD15 expression combined with absence of cytotoxic markers and EMA is strongly associated with DUSP22 rearrangement (PMID: 36453104). This pattern prompted prediction of the FISH result at the time of preliminary diagnosis.

Educational value: This immunophenotypic correlation is not widely recognized outside of T-cell lymphoma subspecialty practice and represents a noteworthy teaching point.

Panel Diagnosis: ALK- ALCL in leukemic phase (DUSP22 rearranged) and HLH

EA4HP26-LYWS-437

Granulomatous inflammation with abundant Langhans giant cells mimicking infection in follicular helper T-cell lymphoma, angioimmunoblastic type.

Dr. Martin Zacharias

Medical University of Graz, Diagnostic and Research Institute of Pathology, Graz, Austria

Case Description

A 78-year-old male presented with weight loss, fatigue and generalized pruritus persisting for weeks. Imaging studies revealed generalized lymphadenopathy and splenomegaly. Excision of an inguinal lymph node conglomerate was performed.

Biopsy Fixation Details

4% formaldehyde solution.

Frozen Tissue Available

No.

Details of Microscopic Findings

Lymph node architecture was largely effaced. Multifocally, with a predilection to high endothelial venules, infiltrates of small to intermediate sized cells with slightly irregular nuclei and partly clear cytoplasm could be seen. Admixed was a polymorphic inflammatory background consisting of histiocytes, reactive lymphocytes, plasma cells, eosinophils and interspersed blasts. The most remarkable feature of this background were numerous Langhans multinucleated giant cells, reminiscent of granulomatous inflammation in infection. However, no obvious microbes could be histologically detected (Ziehl-Neelsen, PAS, Grocott).

Immunophenotype

The described small to intermediate sized cells of the infiltrate were positive for CD2, CD3, CD4, CD279 and CXCL13, but negative for CD7 and CD8. The interspersed blasts expressed CD20, CD22, CD19 and PAX-5, and were positive with EBER-ISH. CD21 and CD23 marked expanded networks of follicular dendritic cells.

Cytogenetics

NA

Molecular Studies

TCR clonality assay results were compatible with a monoclonal rearrangement of T-cell receptor genes. No definitive indication of a monoclonal rearrangement of immunoglobulin heavy and light chains could be detected. The OCA plus DNA assay revealed two likely pathogenic TET2 mutations (VAF 37.82% and 8.56%), and a likely pathogenic DNMT3A mutation (VAF 44.75%).

Mycobacterial PCR and panbacterial PCR (16S gene) were negative.

Proposed Diagnosis

Follicular helper T-cell lymphoma, angioimmunoblastic type.

Interesting Feature(s)

Granulomatous inflammation with abundant Langhans giant cells as mimicker of infection.

Panel Diagnosis: nTFHL/TFHL-AI with granulomata

EA4HP26-LYWS-452**Primary Nodal EBV-Positive T/NK-Cell Lymphoma with Hodgkin-Like features in an immunodeficient patient: A diagnostic challenge.**

Dr. Ifeomachukwu E. Nwosu, [Dr. Lisa Rimsza](#), Dr. Deborah Fuchs

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Case Description

A 45-year-old African American man with advanced HIV infection (CD4 count 68/ μ L) and poor antiretroviral adherence presented with sepsis. Imaging demonstrated diffuse, progressive lymphadenopathy involving nodal chains above and below the diaphragm, with hepatosplenomegaly and pulmonary cavitary lesions. Laboratory evaluation showed marked leukocytosis with neutrophilia, eosinophilia, monocytosis, and lymphocytosis, along with severe anemia and thrombocytosis. EBV PCR revealed an elevated viral load of 24,500 IU/mL, with positive EBV VCA IgG. A right inguinal lymph node biopsy was performed for histologic, flow cytometric, and molecular evaluation

Biopsy Fixation Details

Tissue was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Not performed.

Details of Microscopic Findings

The lymph node was effaced by a heterogeneous population of small to intermediate sized T-lymphocytes with focal proliferation of Hodgkin/Reed–Sternberg–like (HRS-like) cells in a background of eosinophils and plasma cells. The small to intermediate sized T lymphocytes expressed CD2, CD3, and CD7 with CD8 predominance. EBER in situ hybridization was positive, with dual EBER/CD3 confirming EBV-positive T cells. The HRS-like cells expressed CD2, CD3, CD7, CD8 (subset), CD56 (subset), CD30, and cytotoxic markers and were EBER-positive, while negative for CD4, CD15, CD20, PAX5, CD79a, and ALK. AFB, GMS, and CMV stains were negative.

Immunophenotype

Flow cytometry demonstrated a markedly decreased CD4:CD8 ratio (0.34), with a population of surface CD3-negative lymphocytes negative for CD2, CD4, CD5 and CD8. B-lymphocytes are polytypic.

Cytogenetics

Not performed.

Molecular Studies

Molecular studies showed likely pathogenic **PTPRD** and **ARID1A** alterations with clonal T-cell receptor gamma rearrangement and polyclonal immunoglobulin genes.

Proposed Diagnosis

Primary nodal EBV-positive NK/T-cell lymphoma was favored and confirmed on expert review at the National Institutes of Health.

Interesting Feature(s)

Primary nodal EBV-positive T/NK-cell lymphoma is a rare entity, as most EBV-associated T/NK-cell lymphomas present as extranodal (nasal-type) disease. In this case, integrated clinical, histologic, immunophenotypic, and molecular findings supported a diagnosis of primary nodal EBV-positive T/NK-cell lymphoma; however, the morphology was unusual, with prominent CD30-positive Hodgkin/Reed–Sternberg–like cells in a mixed inflammatory background, creating overlap with classic Hodgkin lymphoma.

Although current diagnostic criteria for primary nodal EBV-positive T/NK-cell lymphoma emphasize exclusion of immune deficiency, the lymphoma arose in the setting of severe HIV-associated immunodeficiency. Within the WHO framework, the case also falls within a broader and poorly defined category of lymphomas arising in immune deficiency or dysregulation, for which classification is recommended to follow disease patterns seen in immunocompetent individuals. This principle, however, is difficult to reconcile with diagnostic criteria for primary nodal EBV-positive T/NK-cell lymphoma, and no alternative WHO-defined entity adequately accounts for the clinicopathologic findings.

Overall, this case illustrates challenges in classifying EBV-associated T/NK-cell lymphomas in immunodeficient patients, given morphologic and immunophenotypic overlap between primary lymphomas and immune deficiency–associated processes. T-cell lymphomas are rare in immune deficiency, further limiting available comparative data. These factors highlight the need for further study of this rare entity, including its morphologic spectrum and clinical settings.

Panel Diagnosis: Primary nodal EBV+ NK/T cell lymphoma

A case of an aggressive EBV positive peripheral T cell lymphoma with histiocytes showing hemophagocytosis in a patient with underlying immunodeficiency and HLH

Dr. Arpan Samaddar¹, Dr. Dean Fong²

¹ Oregon Health & Science University, Department of Pathology and Laboratory Medicine, Portland, USA; ² Portland Veteran Affairs Medical Center, Pathology and Laboratory Services, Portland, USA

Case Description

The patient is a 74-year-old man who was admitted with febrile neutropenia and GI symptoms. He had a long-standing history of hematological abnormalities including thrombocytopenia, warm autoimmune hemolytic anemia. He had a history of Common Variable Immunodeficiency with hypogammaglobulinemia as well as a history of heart failure. A year before his admission, he was found to have splenomegaly and diffuse lymphadenopathy. Flow cytometry performed on the peripheral blood and bone marrow revealed a low-level atypical B cell population with absent light chain expression. His blood counts kept declining, and he developed acute renal failure. He met clinical criteria for hemophagocytic lymphohistiocytosis. His condition deteriorated and he passed away 20 days after hospitalization.

Biopsy Fixation Details

Peripheral blood submitted in EDTA; bone marrow aspirate in EDTA; clotted bone marrow aspirate, bone marrow core biopsy and autopsy sections in FFPE blocks.

Frozen Tissue Available

None

Details of Microscopic Findings

Peripheral blood is notable for pancytopenia. The bone marrow aspirate shows atypical large lymphocytes with convoluted nuclei. Histiocytes with hemophagocytosis is seen. The bone marrow core biopsy shows a hypercellular marrow (60%) with an atypical lymphoid infiltrate interstitially and forming aggregates.

Autopsy findings: The T cell lymphoma showed diffuse involvement in the thoracic/abdominal lymph nodes, spleen, bladder, liver, kidney, heart. There was an associated histiocytic infiltrate with evidence of hemophagocytosis.

Immunophenotype

Flow cytometry on the peripheral blood was unremarkable. Flow cytometry on the bone marrow aspirate showed an aberrant T cell population (32% of total events) positive for CD3, CD8, CD56, TCR a/b, decreased CD5, decreased CD7 and with TRBC1 and KIR restriction.

Immunohistochemistry on the bone marrow core biopsy showed the atypical large lymphocytes staining for CD3, CD8, CD56(weakly). CD4 stains background small lymphocytes. They also show loss of CD5. EBER by ISH is positive.

Immunohistochemistry on perihilar lymph node, bladder mucosa obtained during autopsy examination showed that the atypical lymphoid staining for CD3, CD5 and the histiocytic infiltrate was highlighted by CD68.

Cytogenetics

Karyotype: Complex karyotype

50, Y, +X, add (X), (q28),+4,add(7) (q22),add(9)(p22),+13,der(17)t(7;17)(q31;p11.2),+20[7]/49~50,sl,add(4)(q31),-9,add(9),(p22)x2,add(15)(p11.2),add(19)(p13.1)[cp6]/97~100,sl,x2[cp4]/46,XY[3]

Molecular Studies

A comprehensive heme malignancy sequencing panel by NGS was performed. The following alterations of clinical significance were detected:

Gene	Alteration	VAF %
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TP53 p.R273C 20

ARID1A p.N106Kfs*3 16

TET2 p.R1465* 14

KMT2D p.Q2816* 3

Proposed Diagnosis

Peripheral T cell lymphoma, EBV+, common variable immunodeficiency (with prominent histiocytes)

Interesting Feature(s)

This is an interesting case of an aggressive EBV positive peripheral T cell lymphoma with prominent histiocytes showing hemophagocytosis, arising in a patient with an underlying immunodeficiency associated with a clinical diagnosis of HLH. Autopsy showed diffuse involvement by the T cell lymphoma with histiocytes in the microenvironment of the tumor.

Panel Diagnosis: PTCL-NOS in leukemic phase with HLH in the setting of immunodeficiency

EA4HP26-LYWS-456

Cytotoxic PTCL, NOS associated with hemophagocytic lymphohistiocytosis and harbouring a novel *VAV1::EVI5L* fusion

Prof. Laurence de Leval¹, PhD/MD Luis A. Veloza Cabrera¹, Dr. Carmen Barcena²

¹ CHUV, Institute of Pathology, Lausanne, Switzerland; ² Hospital Universitario 12 de Octubre, Departments of Hematology and Pathology, Madrid, Spain

Case Description

A 61-year-old woman presented with B symptoms, and cervical lymphadenopathy. Laboratory test revealed lymphopenia (0.08 G/L), anemia (hemoglobin 97 g/L), thrombocytopenia (117 G/L), elevated ferritin and LDH and hypofibrinogenemia, suggestive of hemophagocytic lymphohistiocytosis (HLH). Brentuximab-based and etoposide chemotherapies were initiated. She presented progressive disease and relapsing HLH 4 months later, which was treated with corticosteroids and etoposide. Romidepsin was attempted as third-line therapy but induced no clinical or laboratory response. The patient developed respiratory failure and died of disease four months after initial diagnosis.

Biopsy Fixation Details

BOM: Acetic acid–zinc–formalin (AZF) fixative.

Lymph node: B-Plus Fix™ and buffered formalin (10%) (specimen submitted).

Autopsy: buffered formalin (10%).

Frozen Tissue Available

Yes, lymph node.

Details of Microscopic Findings

Lymph node (1.5 cm): diffuse proliferation of large lymphoid cells with indented, or lobulated nuclei, vesicular chromatin with prominent nucleoli and scant cytoplasm associated with numerous mitoses and tingible body macrophages and focal necrosis.

BOM: hypercellular bone marrow (45%) with interstitial involvement by lymphoma (35–40%). Numerous mitoses and images of hemophagocytosis were observed. Residual hematopoiesis showed a left-shifted and preserved maturation, no significant dyspoiesis, megakaryocytic hyperplasia and M:E ratio of 1:1. Absence of significant reticulin fibrosis (MF 0–1).

Autopsy showed generalized lymphadenopathy, pericardial and pleural effusions, and splenomegaly (770 g) with splenic infarctions. Histologically, diffuse nodal, splenic and bone marrow infiltration by the T-cell lymphoma with

infiltration of the pulmonary septal microcirculation, associated with hemophagocytosis in the lymph nodes and bone marrow.

Immunophenotype

Lymph node: lymphoma cells were CD3+, CD2+, CD5+, CD7-/+, CD4+, perforin+, granzyme+, TIA-1+/-, p53+ (>70%), CD56-/+, CD30-, CD8-, CD57-, TCRβF1-, TCRδ-, TBET-, CXCR3+/- (dim), GATA3-, CCR4- CD10-, BCL6+/-, PD1+ (dim), CXCL13-, ICOS-, and ALK-, with a high Ki67 index (85%). Residual FDC networks were observed.

BMB: lymphoma cells were CD3+, CD5+, CD4+ (strong), CD2+ (weak), CD7+ (weak to moderate), granzyme B+, and negative for CD8, CD30, and TIA-1. CD68 and CD163 confirmed increased phagocytic macrophages.

EBV (EBER-ISH) negative.

Cytogenetics

Not performed.

Molecular Studies

Lymph node:

PCR: monoclonal T-cell rearrangement.

NGS: pathogenic mutation (class 5) of *STAT3*, two likely pathogenic mutations (class 4) of *TET2*, and mutations of unknown significance (class 3) of *TP53* and *SF3B1*.

NGS Fusion Panel: *VAV1::EVI5L* fusion.

Proposed Diagnosis

Cytotoxic Peripheral T-cell lymphoma NOS with bone marrow involvement and associated hemophagocytosis.

Interesting Feature(s)

Lymphoma-associated HLH is a rare but devastating presentation of lymphoma and portends a very poor prognosis. PTCL is one of the most common lymphoid malignancies associated with HLH, presenting with advance disease stage and aggressive clinical course. Our patient had primary refractory disease.

Fusion transcripts involving *VAV1* have been reported in up to 10% of PTCL, NOS and ALK-negative ALCL with a wide variety of translocation partners. Although, to our knowledge, *EVI5L* has not yet been described as a fusion partner of *VAV1*, the characteristics of the fusion observed in the present case are similar to those reported in the literature and suggest the same activation mechanism, producing a truncation of the C-terminal end of *VAV1* at exon 25 and leading to its constitutive activation.

Panel Diagnosis: Cytotoxic PTCL-NOS with HLH

LYMPHOMA SESSION V | Primary mucosal or cutaneous CD30+ T-cell lymphoma/lymphoproliferative disorders (LPDs); incl. lymphomatoid papulosis (LYP), cutaneous anaplastic large cell lymphoma (ALCL)

EA4HP26-LYWS-26	Cutaneous anaplastic large cell lymphoma with primary subcutaneous presentation
EA4HP26-LYWS-49	An unusual lesion of the submammary region
EA4HP26-LYWS-66	CD30-positive, ALK-negative T cell lymphoproliferative disorder presenting as a rapidly progressing and aggressive abdominal wall mass
EA4HP26-LYWS-69	Primary cutaneous gamma/delta T-cell lymphoma with epidermotropism and CD30 expression
EA4HP26-LYWS-72	Primary cutaneous anaplastic large cell lymphoma with ALK rearrangement
EA4HP26-LYWS-84	Hydroa vacciniforme lymphoproliferative disorder involving oral mucosa
EA4HP26-LYWS-99	ALK positive clonal evolution of mycosis fungoides
EA4HP26-LYWS-100	Paediatric-onset lymphomatoid papulosis
EA4HP26-LYWS-104	A case of pediatric primary cutaneous CD30+ T-cell lymphoproliferative disorder: Lymphomatoid papulosis
EA4HP26-LYWS-125	CNS relapse of primary cutaneous CD30 positive T cell lymphoma
EA4HP26-LYWS-139	A Diagnostic Challenge in a Child with a CD30-Positive Cutaneous T-Cell Lymphoproliferative Disorder and Spontaneous Regression
EA4HP26-LYWS-153	Primary cutaneous anaplastic large cell lymphoma with CD15 expression.
EA4HP26-LYWS-154	Primary cutaneous anaplastic large cell lymphoma carrying a <i>KLF2</i> mutation
EA4HP26-LYWS-155	Recurrent Self-Healing Papulonodular Lesions in a Young Woman: Primary Cutaneous CD30-Positive Lymphomatoid Papulosis
EA4HP26-LYWS-158	Primary cutaneous epidermotropic, cytotoxic, ALK+ T-cell lymphoma
EA4HP26-LYWS-159	Under the eyebrow
EA4HP26-LYWS-162	Primary "Cutaneous" CD30-Positive T-cell Lymphoproliferative Disorder Involving the Tonsil
EA4HP26-LYWS-169	Lymphomatoid Papulosis type E: a case report of a rare entity
EA4HP26-LYWS-177	Pediatric case of borderline type of primary cutaneous CD30+ lymphoproliferative disorder with <i>TNK1::GPS2</i> fusion
EA4HP26-LYWS-178	Case of primary cutaneous CD30+ lymphoproliferative disorder presenting as persistent psoriasiform plaques
EA4HP26-LYWS-180	Two distinct CD30+ cutaneous lymphoproliferative disorders with T-cell differentiation arising simultaneously in a patient with history of Classic Hodgkin lymphoma
EA4HP26-LYWS-181	CD30+ anaplastic large cell lymphoma with rare <i>TNK1::GPS2</i> fusion
EA4HP26-LYWS-183	Post-Therapeutic Phenotypic Alteration in Primary Cutaneous Anaplastic Large Cell Lymphoma: Decreased CD30 Expression and Deep Soft Tissue Extension Mimicking Peripheral T-Cell Lymphoma
EA4HP26-LYWS-198	Lymphomatoid Papulosis with 5' Deletion of <i>DUSP22-IRF4</i> and Gamma-Delta T-Cell Phenotype: A Rarity

EA4HP26-LYWS-206	Multifocal primary cutaneous anaplastic large cell lymphoma (cALCL) with <i>DUSP22</i> rearrangement & p63 upregulation
EA4HP26-LYWS-219	Inflammatory Soil: Lymphomatoid Papulosis type E and Mycosis fungoides preceding Classic Hodgkin Lymphoma in a 30-year-old patient.
EA4HP26-LYWS-222	Primary cutaneous anaplastic large cell lymphoma with the regional lymph node dissemination after the electron radiation treatment in an 11-year-old male
EA4HP26-LYWS-239	CD30-positive primary cutaneous lymphoproliferative disorder, CD30-negative
EA4HP26-LYWS-244	A case of cutaneous CD30-positive lymphoproliferative disorder
EA4HP26-LYWS-263	Primary mucosal CD30+ T-cell lymphoma with striking T-cell reactive population
EA4HP26-LYWS-268	<i>DUSP22</i> -rearranged primary cutaneous CD30-positive T-cell lymphoproliferative disorder
EA4HP26-LYWS-272	Primary Cutaneous Intravascular/Intralymphatic CD30-Positive T-Cell Lymphoproliferative Disorder with <i>DUSP22</i> Translocation
EA4HP26-LYWS-283	The $\gamma\delta$ Dilemma: Distinguishing Transformed Mycosis Fungoides From Primary Cutaneous $\gamma\delta$ T-Cell Lymphoma
EA4HP26-LYWS-286	CD30(+) T-cell lymphoproliferative disorder presenting as nodular lesions of the cheek
EA4HP26-LYWS-290	CD30+ T cell lymphoproliferative disorder
EA4HP26-LYWS-297	ALK(+) anaplastic large cell lymphoma with a primary cutaneous presentation
EA4HP26-LYWS-319	The CD30-positive cutaneous lesion: Anaplastic large cell lymphoma / indeterminate dendritic cell tumor.
EA4HP26-LYWS-327	Recurrent <i>DUSP22-IRF4</i> rearranged lymphomatoid papulosis
EA4HP26-LYWS-338	Granulomatous and eccrinotropic lymphomatoid papulosis
EA4HP26-LYWS-367	Hodgkin-Like Transformation in Mycosis Fungoides? A Composite Lymphoma in Question
EA4HP26-LYWS-374	Cutaneous Anaplastic Large Cell Lymphoma Presenting with Involvement of Nasal Sidewall and Ala
EA4HP26-LYWS-401	Primary cutaneous anaplastic large cell lymphoma presenting as an elbow cyst
EA4HP26-LYWS-405	Lymphomatoid Papulosis
EA4HP26-LYWS-411	Composite lymphoma consisting of a) primary cutaneous CD30+ lymphoproliferative disorder; b) marginal zone lymphoma
EA4HP26-LYWS-423	Primary cutaneous anaplastic large cell lymphoma presenting as a painful left calf mass
EA4HP26-LYWS-431	A rare case of cutaneous ALK-positive anaplastic T cell lymphoma

Cutaneous anaplastic large cell lymphoma with primary subcutaneous presentation

Dr. Kennosuke Karube

Graduate School of Medicine, Nagoya University, Department of Pathology and Laboratory Medicine, Nagoya, Japan

Case Description

A 71-year-old man presented with extensive erythema and subcutaneous nodules involving the entire right lower leg. He had no history of immunosuppressive therapy or the clinical course suggesting mycosis fungoides. No peripheral lymphadenopathy was detected on examination. A cutaneous biopsy was subsequently performed. Computed tomography revealed no lymphadenopathy or visceral organ masses, apart from subcutaneous lesions in the right lower extremity.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The biopsy specimen demonstrated diffuse proliferation of atypical large lymphoid cells, including immunoblasts and anaplastic cells, throughout the subcutaneous adipose tissue. Both the epidermis and dermis were completely spared.

Immunophenotype

The atypical lymphoid cells showed positivity for CD3 (weak), CD4, CD30 (diffuse and strong), TIA-1, granzyme B (partial), perforin (partial), and Ki-67 (approximately 70%). They were negative for CD20, CD5, CD7, CD8, ALK, EBER-ISH, TCR- β , and TCR- δ . CD30 immunostaining highlighted the sparing of the epidermis and dermis, with complete effacement of the subcutaneous adipose tissue.

Cytogenetics

Not done

Molecular Studies

ISH: *DUSP22* (break-apart probe): negative

Proposed Diagnosis

Primary cutaneous anaplastic large cell lymphoma confined to subcutaneous tissue

Interesting Feature(s)

This case represents a CD30-positive T-cell lymphoma strictly confined to the subcutaneous tissue. The prototypical and by far the most common lymphoma with primary subcutaneous involvement is subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Although the clinical presentation and infiltration pattern in the present case suggested SPTCL, the cellular morphology and diffuse CD30 positivity excluded this diagnosis. Primary cutaneous anaplastic large cell lymphoma (pcALCL) typically involves the dermis and may extend into the subcutis, whereas cases with tumor cells confined exclusively to the subcutaneous tissue are exceptionally rare, with only a single case previously reported (Massone *J Cutan Pathol* 2006). The clinicopathological distinction between subcutaneous tissue-confined ALCL, conventional pcALCL, and systemic ALK-negative ALCL requires further clarification.

Panel Diagnosis: C-ALCL

An unusual lesion of the submammary region

Prof. Alberto Zamò¹, Prof. Ioannis Anagnostopoulos¹, Dr. Elena Gerhard-Hartmann¹, Dr. Kathrin Wieczorek², Dr. Mareike Kensity³, Prof. Andreas Rosenwald¹

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Case Description

A 76 year old female patient showed multiple nodular lesions in the skin/subcutis, in part spontaneously healing with residual scars. A lesion from the submammary region was biopsied (present material). This lesion had showed a relatively rapid growth in the two weeks prior to the biopsy, two other smaller lesions are present (not biopsied). A previously performed needle biopsy had resulted in a diagnosis of CD30-positive T-cell lymphoma. The complete excision of the lesion was received as a consultation case.

Biopsy Fixation Details

4% buffered Formaldehyde

Frozen Tissue Available

No

Details of Microscopic Findings

At low power a nodular dermal lesion with rather undefined margins, paler at the periphery is visible. At higher magnification a biphasic pattern, consisting of a central core with prevalence of larger, atypical cells, and smaller cells at the periphery can be appreciated. The smaller cells also display some degree of epidermotropism. Focally, intravascular aggregates of medium/large cells are visible, reminiscent of lesions seen in benign intravascular CD30-positive T-cell proliferation, can be found.

Immunophenotype

Larger cells are positive for CD3, CD30 (strong), CD8 (weak/partial) as well as TR-Beta (weak/partial), and negative for CD7, CD4, TR-Delta, CD56, PD1, EBER. Smaller cells are positive for CD3, CD30 (weak), CD8 as well as TR-Beta, and negative for CD7, CD4, TR-Delta, CD56, PD1, EBER.

Cytogenetics

FISH: *DUSP22* break apart positive (65% of cells display probe breaks).

Molecular Studies

T-cell clonality was demonstrated using the EuroClonality protocol for TRG.

A custom panel sequencing (using the protocol described in Böck et al. (Front Oncol. 2023 Aug 16;13:1231601. doi: 10.3389/fonc.2023.1231601. PMID: 37664054) showed no pathogenic mutations; only a VUS in *GNA13* gene (exon 4, p.Arg335Gly) was discovered, which due to its allele frequency (VAF of 50%) was interpreted as a rare polymorphism.

Proposed Diagnosis

Primary cutaneous CD30-positive lymphoproliferative disorder, specifically lymphomatoid papulosis with *DUSP22* rearrangement.

Interesting Feature(s)

This cases show a prototypical case of lymphomatoid papulosis with *DUSP22* rearrangement, with a typical biphasic morphology and in this case also a biphasic immunophenotype with stronger CD30 expression in the central part of the lesion. The central portion of the lesion is relatively rich in larger cells, reminiscent of an anaplastic large cell lymphoma (hence the original external diagnosis in a core biopsy), while at the periphery a dominance of small-intermediate cells can be appreciated; despite the aggregates of larger cells in the central portion of the lesion, the clinical picture of multiple, spontaneously resolving lesions supports a diagnosis of lymphomatoid papulosis - underlining the importance of a clinical correlation. The presence of focal intravascular aggregates of atypical CD30-

positive cells was not noted in the original description of this disease (PMID: 23648461), but is not a rare feature in primary cutaneous CD30-positive lymphoproliferative disorders (PMID: 26371781).

Panel Diagnosis: LyP with DUSP22 rearrangement

EA4HP26-LYWS-66

CD30-positive, ALK-negative T cell lymphoproliferative disorder presenting as a rapidly progressing and aggressive abdominal wall mass

Dr. Justin Kelley

Vanderbilt University Medical Center, Department of Pathology, Microbiology and Immunology, Nashville, USA

Case Description

54 year old man presented with a large ulcerating left abdominal wall mass that progressed over two years. PET scan within the month was remarkable for a very large and markedly hypermetabolic left anterior abdominal wall mass extending superiorly up to the costochondral margin with regional mildly enlarged and mildly hypermetabolic ipsilateral axillary and subpectoral lymph nodes. He otherwise complains of shooting pain and itching from the mass and denies fevers, chills, night sweats and other lymphadenopathy.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Abdominal wall mass: Sections show multiple fragments of fibrotic and focally necrotic soft tissue extensively involved by an atypical lymphoid infiltrate in a predominantly diffuse pattern with occasional nodules surrounded by fibrosis. The infiltrate is composed of sheets of large cells with moderate cytoplasm, variably irregular to occasionally reniform nuclei, fine chromatin and occasional nucleoli. A polymorphous infiltrate including granulocytes with many eosinophils is also present.

Adjacent axillary lymph node: Sections show a lymph node core focally involved by an atypical lymphoid infiltrate predominantly in subcortical sinuses and focally in interstitial sinuses. The infiltrate is also associated with mixed inflammation including many eosinophils. The atypical lymphoid cells are large in size with moderate cytoplasm and variably irregular to occasionally eccentric and reniform nuclei.

Immunophenotype

Abdominal wall mass: The large atypical cells are positive for CD3, CD4 (subset), CD15 (strong diffuse), CD30 (strong diffuse), CD43 (small subset), BCL2, MUM1 and CMYC. The cells are negative for CD5, CD7, CD10, CD20, CD34, CD56, CD68, CD117, CD138, CD163, ALK, BCL6, cyclin D1, EBER ISH, EMA, MPO and PAX5. Ki67 proliferative index is high (95%). CD21 does not show FDC meshworks. Flow cytometry was not performed.

Adjacent axillary lymph node: The atypical cells are positive for CD3, CD4 (subset), CD30 (strong), CD43 and EMA (focal). The cells are negative for CD5, CD8 and CD20. Concurrent flow cytometry was negative for lymphoma.

Cytogenetics

ALCL FISH panel (ALK, TP63, TBL1XR1::TP63, DUSP22-IRF4) is negative.

Molecular Studies

None

Proposed Diagnosis

CD30-positive, ALK-negative T cell lymphoproliferative disorder, favor primary cutaneous anaplastic large cell lymphoma

Interesting Feature(s)

The history of an ulcerating and worsening abdominal wall mass raises the possibility of cutaneous origin, which would be most consistent with ALK-negative anaplastic large cell lymphoma (ALCL). The absence of ALK-rearrangement and systemic involvement as well as the absence waxing and waning lesion disfavor systemic ALCL and lymphomatoid papulosis, respectively. Furthermore, the absence of systemic lymphadenopathy and only focal involvement in the adjacent lymph node also favor draining of a primary cutaneous rather than systemic lymphoma. However, the aggressive and rapidly progressive clinical course overlapped with a more aggressive-type systemic lymphoma, complicating clinical management.

Panel Diagnosis: C-ALCL

EA4HP26-LYWS-69

Primary cutaneous gamma/delta T-cell lymphoma with epidermotropism and CD30 expression

Dr. Gayathri Kollipara, Dr. Yi Sun

Rutgers Robert Wood Johnson University Hospital, pathology, New Brunswick, USA

Case Description

The patient is a 56-year-old man with history of skin changes that have progressively worsened over the last 3 years. There is extensive cutaneous involvement from patches to plaques to nodules and exophytic tumors on his neck, trunk, upper and lower extremities including heels. The tumorous lesions ranging from 2- 6 cm mostly in annular configuration and raised violaceous border, associated with scar formation; covering approximately 70 to 75% of the patient's body surface area. A prior biopsy performed showed CD30 positive lymphoproliferative disorder with large cells, and a diagnosis of lymphomatoid papulosis, type D was favored. He was initially treated with Bexarotene with partial response, but some of the tumorous lesions progressed. A repeat biopsy was performed.

Biopsy Fixation Details

The tissue was fixed in 10% formalin for at least 6 hours before processing

Frozen Tissue Available

N/A

Details of Microscopic Findings

H&E stained sections show hyperplastic squamous epithelium infiltrated by atypical lymphocytes that are medium to large in size with irregular nuclei, variably distinct nucleoli and clear to pale cytoplasm. The atypical infiltrate predominantly involves the epidermis with microabscesses present.

Immunophenotype

By immunostains, the atypical lymphocytes are positive for CD3, CD2, CD8, CD7, CD30, MUM1 (subset, variable), while negative for CD20, PAX5, CD5, CD4, CD25 and CD56. CD20 and PAX5 highlight rare small B cells. Ki-67 shows about 50% proliferation rate. EBER ISH is negative.

Cytogenetics

FISH was negative for ALK and DUSP22 rearrangements.

Molecular Studies

T-cell gene rearrangement studies of both prior and current biopsies are positive and show similar clonal peaks

Proposed Diagnosis

Primary cutaneous gamma/delta T-cell lymphoma, with epidermotropism and CD30 expression

Interesting Feature(s)

This case represents an unusual and rare primary cutaneous T-cell lymphoma with γ/δ phenotype, characterized by prominent epidermotropism, extensive CD30 expression, and large-cell morphology. The initial histologic and immunophenotypic findings raised a differential diagnosis of a CD30-positive cutaneous lymphoproliferative disorder, favoring lymphomatoid papulosis (type D). However, the patient's subsequent clinical behavior was discordant with this diagnosis, showing only a partial initial response followed by progression to multifocal tumorous and ulcerating disease.

Over a three-year period, the patient required multiple lines of systemic therapy, including chemotherapy, immunotherapy, and targeted therapy, each producing transient clinical responses followed by disease progression. Most recently, the patient has demonstrated clinical improvement on a clinical trial combining EZH2 and HDAC inhibitors, underscoring the aggressive and treatment-refractory nature of the disease.

Notably, this case is also atypical for classic primary cutaneous γ/δ T-cell lymphoma, which is usually characterized by a rapidly progressive and highly aggressive clinical course. In contrast, this patient exhibited a relatively indolent initial presentation with a prolonged cutaneous phase and partial therapeutic responsiveness, followed by later disease acceleration, highlighting the clinical heterogeneity of γ/δ cutaneous T-cell lymphomas.

This case emphasizes the importance of integrating morphology, immunophenotype, and longitudinal clinical presentation in the classification of cutaneous T-cell lymphomas and illustrates the expanding clinicopathologic spectrum of primary cutaneous γ/δ T-cell lymphomas.

Panel Diagnosis: Primary cutaneous gamma/delta T-cell lymphoma

EA4HP26-LYWS-72

Primary cutaneous anaplastic large cell lymphoma with ALK rearrangement

Prof. Celine Bossard¹, Dr. Nicolas Josselin¹, Dr. Anne Moreau³, Prof. Laurence Lamant⁴, Dr. Yannick Le Bris⁵, Prof. Gaëlle Quereux⁶

¹ IHP group, Pathology, Nantes, France; ² IHP group, Pathology, Nantes, France; ³ CHD Vendée, Pathology, La Roche sur Yon, France; ⁴ CHU Toulouse, Pathology, Toulouse, France; ⁵ CHU Nantes, Hematology biology, Nantes, France; ⁶ CHU Nantes, Dermatology, Nantes, France

Case Description

A 32-year old woman without any medical history, was admitted to hospital for an ulcerated cutaneous tumor of 5 x 4 cm in the left submammary fold associated with several smaller papular and purplish multifocal (trunk, right buttock, left axilla) cutaneous lesions. The main lesion appeared brutally 1 month earlier as an erythematous infiltrated centimetric thick plaque, and progress rapidly in 1 month to become a ulcerative tumor mass, associated with multicentric papules without any systemic symptom. FDG PET-CT revealed a high avidity of all lesions, without lymphadenopathy.

The cutaneous biopsy (breast) revealed an extensive and diffuse dermal infiltrate, sparing the epidermis but in close contact with, and composed almost of medium/large anaplastic cells, associated with some eosinophils. Phenotypically, the medium/large anaplastic cells diffusely and strongly expressed CD30 as well as CD4 and CD5, but were CD2 (40%), CD3 (40%) CD7 and CD8 negative. Some large atypical CD30+ cells were found within epidermis. Expression of granzyme B was heterogeneous, as well as EMA (faint in 20% of cells), but ALK was strongly expressed (cytoplasmic and nuclear, 80% of tumor cells). Molecular study revealed a clonal TCR γ rearrangement in the skin. Fluorescent in situ hybridization revealed a ALK (2p23) rearrangement in 70-80% of tumor cells.

Clinical evolution/treatment : The breast nodule as well as all other smaller cutaneous lesions have spontaneously disappeared without any treatment in 1 month, and the patient is in complete remission after 9 months of follow up.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

no

Details of Microscopic Findings

The cutaneous biopsy (breast) revealed an extensive and diffuse dermal infiltrate, sparing the epidermis but in close contact with, and composed almost of medium/large anaplastic cells, associated with some eosinophils.

Immunophenotype

Phenotypically, the medium/large anaplastic cells diffusely and strongly expressed CD30 as well as CD4 and CD5, but were CD2 (40%), CD3 (40%) CD7 and CD8 negative. Some large atypical CD30+ cells were found within epidermis. Expression of granzyme B was heterogeneous, as well as EMA (faint in 20% of cells), but ALK was strongly expressed (cytoplasmic and nuclear, 80% of tumor cells).

Cytogenetics

Fluorescent in situ hybridization revealed a ALK (2p23) rearrangement in 70-80% of tumor cells.

Molecular Studies

Molecular study revealed a clonal TCR g rearrangement in the skin.

Proposed Diagnosis

C-ALCL with ALK rearrangement or ALK+ skin-limited ALCL.

Interesting Feature(s)

ALK expression and rearrangement in a cutaneous CD30- positive T-cell lymphoproliferative disorder/ALCL without clinical/radiological argument for a systemic ALCL. Thus a rare case of C-ALCL with ALK rearrangement, in a young woman of 32yo that followed the typical benign clinical course of a CD30+ LPD.

Panel Diagnosis: C-ALCL with ALK (2p23) rearrangement

EA4HP26-LYWS-84

Hydroa vacciniforme lymphoproliferative disorder involving oral mucosa

Dr. Chuan Chen, Dr. Angela M. Collie, Dr. Rebecca L. King, Dr. Dan P. Larson

Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, USA

Case Description

An 11-year-old Caucasian girl presented to our institution with a persistent, painful oral lesion on the upper left gingiva for one month. She had a history of hydroa vacciniforme lymphoproliferative disorder (HVLPD) since age five, with recurrent breakouts previously limited to the skin of the face and arms, managed conservatively. The current oral lesion began as a small dot and progressively enlarged, with a whitish yellow appearance similar to a canker sore, affecting the adjacent tooth and surrounding areas. Initial treatment with antibiotics and tooth extraction did not result in improvement. She had no cutaneous lesions, lymphadenopathy, jaundice, bleeding or bruising, or B symptoms. A whole body PET-CT showed no other lesions. Peripheral blood labs were notable for low-level EBV DNA detected by quantitative PCR (66 IU/mL); EBV IgG was present by serology and EBV IgM was absent. A biopsy was performed.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the gingiva biopsy show squamous mucosa with intraepidermal vesiculation. Within the epithelium, there are small lymphocytes and scattered eosinophils. Beneath the epithelium, there is an atypical lymphoid infiltrate characterized by aggregates of large atypical lymphoid cells with irregular nuclear contours, reticular chromatin, prominent nucleoli, and abundant amphophilic cytoplasm admixed with frequent eosinophils. Some angiocentric growth is present.

Immunophenotype

Atypical lymphoid cells express CD2, CD3, CD5 (partial), CD30 (variable up to 70%), TCR Delta, TIA-1, granzyme B, and are positive for EBER by ISH. They are negative for CD4, CD7, CD8, CD56, ALK, and TCR Beta F1.

Cytogenetics

N/A

Molecular Studies

Clonal T-cell receptor gene rearrangement

Proposed Diagnosis

Hydroa vacciniforme lymphoproliferative disorder

Interesting Feature(s)

This case represents an uncommon presentation of a clinically-indolent (classic) HV-LPD involving oral mucosa that showed significant cytologic atypia and aberrant immunophenotype. This lesion was initially interpreted as progressive HVLDP (or other aggressive lymphoma) based on the histopathologic features alone, and chemotherapy was planned even with knowledge of the patient's history of HVLDP. Upon biopsy and clinical review at our institution, it was emphasized that the pathologic features alone do not warrant aggressive therapy in the correct clinical setting that includes the absence of progressive or systemic disease. The mucosal lesion resolved after 5 days on an oral steroid and did not recur at 6 months follow up. Clinical correlation is essential in cases of HVLDP that might show a morphologic and phenotypic spectrum overlapping with that of more common aggressive lymphomas.

Panel Diagnosis: HV-LPD

EA4HP26-LYWS-99

ALK positive clonal evolution of mycosis fungoides

Dr. Ye L. Hock¹, Dr. Matthew Pugh¹, Dr. Angelia Ong², Dr. Louise Edwards³

¹ University Hospitals Birmingham NHS Trust, Cellular Pathology, Queen Elizabeth Hospital, Birmingham, UK; ² Christie Hospital, Histopathology, Manchester, UK; ³ University Hospital North Midlands, Histopathology, Stoke-on-Trent, UK

Case Description

A 54-year-old Caucasian female with long-standing psoriasis/eczema had relapsing and remitting itchy skin rash in the last few years. She developed an abdominal skin nodule over 18-months and an excision was performed (submitted). PET-CT showed mildly FDG avid cutaneous thickening & very mild axillary nodal uptake. Dermatology review noted typical features of mycosis fungoides (MF) & skin punch biopsies were also supportive (submitted). Lymph node core biopsy showed dermatopathic lymphadenopathy only. She was managed as primary cutaneous ALK+ ALCL (ALK+ c-ALCL) & co-existing MF (T2a N0 B0 M0). She received methotrexate & prednisolone for MF. Her skin rash flared up on reducing steroid but her abdominal skin lesion was in remission following local excision only

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Abdominal skin nodule: A diffuse solid atypical large lymphoid infiltrate without epidermotropism but epidermis is ulcerated

Skin punch biopsy: Marked epidermotropism by mild atypical small lymphoid cells with prominent basal tagging. No obvious large cell component

Immunophenotype

Skin nodule

+ve: CD30, CD25, Mum 1, CD4, Granzyme B, EMA, ALK (cytoplasmic)

-ve: CD43, CD3, CD2, CD5, CD7, CD8, CCR4, GATA3, BF1, TCR delta

Skin punch

+ve: CD3, BF1, CD4;

A small subpopulation: CD30, CD25 and ALK (cytoplasmic)

-ve: CD2, CD5, CD7, EBER

Cytogenetics

FISH (both biopsies): ALK rearranged but no DUSP22/IRF4 or TP63 rearrangement

Molecular Studies

EuroClonality-NDC (abdominal nodule):

CCND3 rearrangement (VAF 68%)

ALK::AUT52 (t;2:7) (VAF 3%)

Clonal TCRA rearrangement

MF punch biopsies: Failed

Proposed Diagnosis

ALK positive clonal evolution of mycosis fungoides resulting in ALK+ anaplastic large cell lymphoma-like CD30+ large cell transformation

Interesting Feature(s)

ALK+ c-ALCL is rare but well-described and many cases show variant ALK translocation. Primary cutaneous CD30+ lymphoproliferative disorder (LPD) can develop in MF and can be clonally related or unrelated to MF. Differentiating c-ALCL from large cell transformation of MF (LC-MF) can be challenging histologically. Extensive loss of T-cell antigens and GATA3 negativity are said to favour primary cutaneous CD30+ LPD/c-ALCL over transformed MF (Cancers 2023, 15(16), 4098). Clinical correlation is also felt to be essential to make the distinction.

The clinical course in our patient appears indolent with ALK+ nodular disease being treated successfully by local excision only, more in keeping with c-ALCL but the follow up was short (<1 year). The phenotype (total T-cell antigen loss & GATA3 -ve) would also support this. However, review of MF diagnostic skin biopsy showed scattered CD30+, ALK+(cytoplasmic) cells and FISH confirmed ALK rearrangement. A recent literature review (Virchows Archiv; 2024;485, 417-425) noted 7 cases of ALK+ c-ALCL with MF-like clinical presentation although 2 cases had nodal disease and 2 had an aggressive progression. Interestingly, clinical MF-like cases were managed with MF-type therapeutic approach. Although MF-like presentation of ALK+ c-ALCL is possible, in view of totally different histological picture between the 2 biopsies and the 2nd biopsy containing only scant ALK+ CD30+ cells (<< 75% required for the diagnosis of ALCL) in the background typical for MF, we hypothesize this to be ALK+ clonal evolution of MF resulting in ALK+, CD30+ large cell transformation in the abdominal nodule. Clinical behaviour is also typical for c-ALCL in abdominal nodule and MF in general further supporting this. Although LC-MF usually has a poor prognosis, indolent cases have been described.

Panel Diagnosis: ALK positive clonal evolution of MF with ALCL-like large cell transformation

Paediatric-onset lymphomatoid papulosis**Dr. Ye L. Hock***University Hospitals Birmingham NHS Trust, Cellular Pathology, Queen Elizabeth Hospital, Birmingham, UK***Case Description**

A 9 year-old male presented with outbreaks of skin lesions on trunk and thigh of 3 months duration. These increased in size and some ulcerated but healed over time with some scarring. There were no associated symptoms and he was otherwise well. Punch biopsy of skin lesion was performed. He was originally treated with clarithromycin, and changed over to double base gel and synalar C after no response to Mometasone fuorate 0.1%. He finally seemed to respond well to skin directed phototherapy (narrowband UVB) with no relapse after ~5 years follow-up.

Biopsy Fixation Details

10% buffered formaldehyde

Frozen Tissue Available

No

Details of Microscopic Findings

A heavy nodular polymorphic infiltrate composed of abundant eosinophils, some neutrophils and histiocytes admixed with large atypical nucleolated cells including some with horseshoe nuclei.

Immunophenotype

Positive: CD30, CD25, Mum 1, CD2, CD4, TIA1, Granzyme B, CD45, CD43, CD2, CD5, Mum 1

Negative: CD3, ALK, EBER, CD68 (KP1 and PGM1), CD20, CD1a, p63, Langerin

Cytogenetics

FISH for DUSP22/IRF4 or TP63 rearrangement: Uninterpretable due to scant CD30+ cells with background fluorescence in neutrophils

Molecular Studies

Genomic analysis using EuroClonality-NDC showed no sequence or structural variants but low level clonal TRA(TRA17/TRAJ33, TRA121/TRAJ22), TRB (TRBV19/TRBJ1-2) and TRG (TRGV4/TRGJ2) rearrangements in polyclonal background detected. Few or no TCRD rearrangement. No clonal IGH, IGK or IGL rearrangement.

Proposed Diagnosis

CD30 positive lymphoproliferative disorder most in keeping with lymphomatoid papulosis type A

Interesting Feature(s)

Although lymphomatoid papulosis (LyP) typically occurs in adult patients with the peak incidence in the fifth decades, 'paediatric-onset LyP' is well-described with a mean age of onset at 7 years and male/female ratio of 2:1. In 26% of paediatric patients, this was initially misdiagnosed with the mean interval between the onset and the LyP diagnosis of 1.3 years. Although paediatric LyP has the overall survival rate of 100% after 5-year follow-up, associated haematological malignancy was detected in 10% of affected individuals (significantly higher risk than the general population) in a recent multi-centre study (1). Hence, accurate and timely diagnosis is essential for the correct management and long-term follow-up of these patients.

Ref: Br J Dermatol. 2024; 191(2):233-242

Panel Diagnosis: LyP type A, paediatric-onset

A case of pediatric primary cutaneous CD30+ T-cell lymphoproliferative disorder: Lymphomatoid papulosis

Jingwei Li, David D. Grier, Robert B. Lersbach

Cincinnati Children's Hospital Medical Center, Division of Pathology and Laboratory Medicine, Cincinnati, USA

Case Description

A previously healthy 8-year-old female developed several pink-red skin papules with gold-colored crusting. These solitary shoulders, thigh and facial skin lesions persisted for one to two months in duration and older lesions were stable in size with show erosions. Topical corticosteroid or antibiotic therapies showed no significant clinical improvement. Physical examination showed a 1.0 cm red round plaque with a dark brown to black ulcerated center located on her right thigh.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No

Details of Microscopic Findings

The skin lesion biopsy showed a dense mixed superficial and deep dermal lymphohistiocytic infiltrate associated with areas of collagen necrobiosis with a few intermixed eosinophils. There was marked edema of the papillary dermis with associated subepidermal clefting and focal epidermal full-thickness necrosis. There is a transdermal infiltrate of atypical lymphoid cells, including frequent large cells and rare anaplastic appearing cells, seen singly and large aggregates.

Immunophenotype

The atypical lymphoid cells were positive for CD3, CD5, CD4, CD30 and were negative for CD20, CD7, CD8, ALK and CD56. CD20 labels rare B-cells. Occasional CD7 or CD8 positive T-cells are present. Frequent admixed histiocytes were present, confirmed by the CD163 stain. Special stains for microorganisms were negative. In situ hybridization for EBV virus encoding region (EBER) was negative.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Differential diagnoses included lymphomatoid papulosis (type C) and primary cutaneous anaplastic large cell lymphoma. The final classification required correlation with additional clinical and radiological findings. Further physical examination showed no evidence of lymphadenopathy or organomegaly, which was also confirmed by radiological studies. A complete blood count with differential was within normal limits. A diagnosis of lymphomatoid papulosis (LyP) was made based on the overall clinical, radiological and histological findings.

Interesting Feature(s)

The patient was treated with oral methotrexate and her skin lesions responded well to this therapy. Over the next two years, multiple trials to wean off therapy resulted in worsening skin papules. The patient remains on methotrexate with good control of disease. LyP accounts for 15.9–47% of all pediatric cutaneous lymphoproliferative disorders. Histologic pattern type A is the most commonly seen in pediatric LyP. Similar to adults, pediatric LyP patients have good prognosis with 100% overall survival. However, LyP is associated with increased risk of hematolymphoid malignancies before, concomitant or after the LyP diagnosis in 15.5% - 52% of adult patients. A study in 2020 reported a cohort of 27 pediatric and adolescent LyP patients without subsequent hematolymphoid malignancies. However, there are also rare case reports and series with pediatric and adolescent LyP patients subsequently developing hematolymphoid malignancies including anaplastic large cell lymphoma, Hodgkin lymphoma, non-

Hodgkin lymphoma, mycosis fungoides and mastocytosis. In 2024, A larger cohort showed 7 of 73 pediatric LyP patients subsequently developed hematologic malignancies including acute myeloid leukemia. Interestingly, rare cases of subsequent mycosis fungoides contained the same T-cell clone as seen in LyP, raising the possibility of these lesions might be part of the same disease spectrum. In summary, pediatric LyP may be less commonly associated with hematolymphoid malignancies compared with adults, but long-term clinical follow-up is still warranted.

Panel Diagnosis: LyP type C, pediatric-onset

EA4HP26-LYWS-125

CNS relapse of primary cutaneous CD30 positive T cell lymphoma

Dr. Silvia T. Bunting¹, Dr. Nalin LeeLation²

¹ Vanderbilt University Medical Center, Pathology, Microbiology and Immunology/Hematopathology/Vanderbilt University of Medical Sciences, Nashville, USA; ² Vanderbilt University Medical Center, Pathology, Microbiology and Immunology/Neuropathology/Vanderbilt University of Medical Sciences, Nashville, USA

Case Description

69 y.o. female with history of primary cutaneous anaplastic large cell lymphoma, initially presenting in her elbow in 2005 s/p resection, radiation. The tumor recurred in 2017, s/p resection, and recurred on 2022 s/p resection and immunotherapy. The patient presented 2 weeks of left sided weakness and new left-sided vision loss. CT and MRI showed a 4.9 x 2.8 x 3.8 cm heterogenous peripherally enhancing mass centered along the R paracentral lobule with extensive surrounding region of hypoattenuation involving the R frontal, parietal lobes and R motor cortex, associated mass effect resulting in effacement of the R hemispheric sulci, partial effacement of the R lateral ventricle, and ~2mm leftward midline shift. There was no evidence of acute hemorrhage, infarct, or hydrocephalus. CT chest did not reveal evidence of metastatic disease.

She had a history of several GTC seizures on 3/2025 and got an MRI brain, was started on prednisone and Keppra. She also underwent a PET scan on 3/2025. She did not have left-sided weakness at that time. She saw a neurologist 2 weeks ago for the new left-side weakness and underwent lumbar puncture. She was transferred here for a second opinion for her worsening symptoms.

A frontal craniotomy for open biopsy was performed. Intraoperative consultation showed involvement by lymphoma. A portion of the tissue was sent for flow cytometry analysis. The patient was treated with methotrexate post surgery and was transferred to skill nursing facility for further management.

Biopsy Fixation Details

The tissue was fixed in 10% buffered formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Sections demonstrate a fragment of brain parenchyma involved by a sheet of intermediate size atypical cells with slightly irregular nuclear contour, minimal cytoplasm, vesicular chromatin, and prominent nucleoli.

Immunophenotype

By immunohistochemistry, the cells are positive for CD3, CD4, CD30, and CD45; and negative for CD5, CD7, CD20, ALK, TIA-1, PD-1, BCL-6, CD10, and GFAP.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

CNS involvement by CD30 Positive T cell lymphoma, relapsed.

Interesting Feature(s)

This is a rare case CNS relaps after multiple cutaneous relapses with primary cutaneous CD30 positive ALK negative T cell lymphoma. There were a few reports of cutaneous T cell lymphoma with CNS metastasis with or without extra-cutaneous metastasis prior to or synchronous CNS metastasis. These include mycosis fungoides, primary cutaneous anaplastic large cell lymphomas or mature T/NK cell lymphomas. CNS involvement by cutaneous T cell lymphomas is rare and devastating events with poor prognosis. There is no standardized approach regarding the diagnosis or treatments for the CNS involvement. In addition, more work is needed to understand the biology of the tumor and identify clinicopathologic risk factors which might benefit from CNS prophylaxis and more aggressive systemic therapy.

Panel Diagnosis: CD30+ large T-cell lymphoma, relation with C-ALCL unconfirmed

EA4HP26-LYWS-139

A Diagnostic Challenge in a Child with a CD30-Positive Cutaneous T-Cell Lymphoproliferative Disorder and Spontaneous Regression

Dr. Chao Chen¹, Dr. Priyanka Nanjireddy², Dr. Matthew Koo¹, Dr. Jonathan Said¹, [Dr. Christian Hirt](#)¹

¹ UCLA David Geffen School of Medicine, Pathology and Laboratory Medicine, Los Angeles, USA; ² UCLA David Geffen School of Medicine, Pediatric Hematology/Oncology, Los Angeles, USA

Case Description

A 10-year-old boy with autism spectrum disorder and ADHD presented with molluscum contagiosum and a 4-month history of a painful left groin mass. His history was notable for prior hydrocele repair at age 4 and a left buttock abscess. Physical examination revealed molluscum lesions, worsen over time with abscess formation and an ulcerated plaque on the left inner thigh with associated inguinal lymphadenopathy. Despite oral antibiotics, the groin remained tender, prompting biopsy of the cutaneous lesion.

Biopsy Fixation Details

Skin shave biopsy (1.6 x 1.0 x 0.3 cm) with epidermis raised, friable, tan-pink, and a depressed, tan gray area measuring 0.5 x 0.5 x 0.1 cm.

The specimen is serially sectioned and entirely submitted in a mesh bag and in Formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Low power: a superficial and partially ulcerated shave specimen with epidermal loss and underlying granulation tissue. Within the superficial and dermis, there is a dense, diffuse lymphoid infiltrate.

High power: the lymphoid infiltrate is composed of a mixed population of lymphoid cells with a conspicuous component of medium-to-large atypical lymphocytes. These large cells display irregular nuclear contours, vesicular chromatin, and occasional prominent nucleoli. Scattered cells demonstrate anaplastic morphology with abundant cytoplasm. Numerous mitotic figures and apoptotic bodies are present.

Immunophenotype

ANTIBODY RESULT (IN CELLS OF INTEREST)

CD30 Positive (diffuse strong membranous staining with Golgi accentuation)

ALK Negative

CD3	Negative on majority of cells
CD20	Negative
CD5	Negative on majority of cells
CD2	Positive
CD7	Positive
CD4	Negative for definitive expression
CD8	Negative
TCR beta F1	Positive
TCR gamma	Negative
TIA1	Positive, subset weak
Granzyme	Positive
CD45	Positive, subset
CD43	Positive
EBER ISH	Negative for definitive expression
CD31	Negative
CD34	Negative
CD117	Negative
CD68	Negative
PU.1	Negative, stains histiocytes
Langerin	Negative
CD1a	Negative

Cytogenetics

Test	Interpretation	Signal	Pattern	Abnormality Identified	% Cutoff
ALK for Lymphoma	Not Detected	2F		None	– N/A
TP63 for ALCL	Not Detected	0ROG	>=1F	None	– N/A
TBL1XR1/TP63 for ALCL	Not Detected	>=1R	>=1GOF	None	– N/A
DUSP22-IRF4 (6p25.3) Rearrangement	Not Detected	2F		None	– N/A

Molecular Studies

Clonal T-cell gene rearrangement observed for *TRG* locus

Proposed Diagnosis

SKIN LESION, THIGH (SHAVE BIOPSY):

- CD30-positive T-cell lymphoproliferative disorder (see comment)

COMMENT:

The differential diagnosis based on this superficial shave biopsy includes lymphomatoid papulosis type C and anaplastic large cell lymphoma.

Interesting Feature(s)

- Limitations of superficial biopsies for definite diagnosis
- Diffuse CD30 expression and positive TCR clonality but benign clinical course
- Overlap between lymphomatoid papulosis and cutaneous anaplastic large cell lymphoma

Panel Diagnosis: spectrum/borderline or C-ALCL

EA4HP26-LYWS-153

Primary cutaneous anaplastic large cell lymphoma with CD15 expression.

Dr. Sahil Chaudhary, Dr. Jinbo Fan, **Dr. Ifeyinwa E. Obiorah**

University of Virginia Health, Charlottesville, USA

Case Description

The patient is a 64-year-old man with a history of cutaneous lymphoma, who presented to our institution for management of his disorder. Six years prior he had multiple skin biopsies that were diagnosed as lymphomatoid papulosis which has been stabilized with weekly methotrexate. Presently patient presents with fatigue, night sweats, scrotal swelling and multiple nodules on the left upper extremity. PET/CT scan detected hypermetabolic multistation lymphadenopathy in abdomen, thorax, lower neck (SUV max 24). Biopsy of the skin and the right inguinal lymph node is obtained. The patient was treated with multiple cycles of Bv-CHP. Five months later, the patient's symptoms have improved. PET/CT scan is negative and patient has no active skin disease.

Biopsy Fixation Details

The skin and lymph node were fixed in formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

The skin biopsy shows a superficial and deep dermal infiltrate of predominantly intermediate-sized lymphoid cells with irregular nuclear contours with an interstitial distribution. There are also scattered pleomorphic large cells. These atypical cells are admixed among a background of small lymphocytes, eosinophils and histiocytes. Histologic sections of the lymph node show thin cores with involvement by an atypical lymphoid proliferation. The infiltrate is composed of medium to large atypical lymphoid cells with vesicular nuclei and prominent nucleoli and occasional bi/multinucleation. There is a background of small lymphocytes, eosinophils and some histiocytes

Immunophenotype

The atypical cells in the skin are highlighted by CD30. They positive for CD2, CD4, CD5, CD15 (focal), and negative for CD3, CD7, CD8, ALK1 and TCRD. TCRBF1 appears to stain the small background T cells. A subset of the T cells appear positive for granzyme B and perforin. PAX5 and CD20 stain rare scattered B cells. Ki-67 shows a moderately high proliferative rate (40%). In the lymph node, the large atypical cells are positive for CD30, CD15, CD2 and focal expression of CD2. The atypical cells were negative for CD3, CD5, CD7, CD8, PAX5, CD3, CD45, ALK1, BOB1, OCT2, CD79a, GATA3, STAT6, CD43, melan-A, S100, HMB45 and keratin. Ki-67 is positive in the large atypical cells. EBV RNA stain is negative.

Cytogenetics

: FISH studies were negative for DUSP22 gene rearrangements.

Molecular Studies

PCR studies detected T cell receptor clonal peaks (192bp and 194 bp) in the skin biopsy.

Proposed Diagnosis

Primary cutaneous anaplastic large cell lymphoma with CD15 expression.

Interesting Feature(s)

The patient has a long-standing history of lymphomatoid papulosis controlled with methotrexate, followed years later by development of systemic, PET-avid multistation lymphadenopathy and B symptoms, highlighting disease progression within the spectrum of CD30-positive cutaneous lymphoproliferative disorders

Both skin and lymph node biopsies show a CD30-positive atypical lymphoid proliferation with overlapping morphology and immunophenotype, supporting a unified disease process with secondary nodal involvement rather than a de novo unrelated lymphoma.

The neoplastic cells demonstrate an unusual immunoprofile with CD30 and CD15 expression, loss of pan-T-cell markers, absence of B-cell markers and EBV negativity, creating a challenging differential diagnosis that includes ALCL and classic Hodgkin lymphoma mimics.

Treatment with Bv-CHP resulted in rapid clinical improvement, resolution of PET-avid disease, and clearance of skin lesions, underscoring the therapeutic relevance of CD30 expression and supporting classification within a CD30-positive T-cell lymphoproliferative spectrum.

Panel Diagnosis: LyP progressing to CD15+ ALCL with systemic localization

EA4HP26-LYWS-154

Primary cutaneous anaplastic large cell lymphoma carrying a *KLF2* mutation

Xavier Ara-Mancebo, Andrea Molina-Alvarez, Ivonne Vazquez, Carmen Lome-Maldonado, Luis Colomo

Hospital del Mar, University Pompeu Fabra, Barcelona, Spain

Case Description

57 y-old female with no relevant previous medical history.

Presented in June 2019 with an abdominal plaque of 6x3 cm (biopsy performed) and axillary skin nodule 3x2 cm, being diagnosed of Primary cutaneous anaplastic large cell lymphoma (ALCL). The patient was treated with methotrexate (MTX) and radiotherapy achieving complete remission (CR), but experienced multiple relapses to date:

- February 2020: nodule (ALCL) in the back à Mtx and CR
- May 2021: gluteal nodule 3x2.5 cm (ALCL)à starts Brentuximab, and appear lesions of Lymphomatoid papulosis (LyP) in the face and arms à nodule in CR and new LyP lesions in arms, finally in CR in September 2021
- January 2022: axillary nodule à Mtx and CR
- August 2023: nodules in the shoulder, neck and breast area (ALCL), and LyP lesions in the arms à Mtx and CR
- May 2024: no skin disease, appear cervical and submandibular LN à ALCL à CR after brentuximab
- November 2024: nodules in breast, retroauricular and chin à brentuximab and CR, starts again Mtx
- June 2025: ALCL nodules in trunk and arm, and LyP lesion in arm à in treatment with Mtx
- October 2025: new ALCL skin lesions in the back, abdomen and inguinal area à starts again brentuximab à appear multiple LyP lesions in arms and legs during November 2025
- January 2026: under treatment with brentuximab, minimal skin lesions of ALCL and Lyp.

Biopsy Fixation Details

4% Formaldehyde solution (0.05M phosphate buffer) for 24 hours.

Frozen Tissue Available

Yes

Details of Microscopic Findings

All biopsies shared morphological and immunophenotypical features. On histological grounds, the tumor cells were large and showed features of ALCL. Apoptotic bodies and mitotic features were frequent.

Immunophenotype

The tumor cells expressed strong CD30, as well as CD3 and CD7 (partial loss), and GATA3. Additional markers were all negative: CD56, TIA-1, Granzyme B, perforin, T-bet, CD20, CD79a, EBERs, CD68, CD14, CD163. Ki67 index was over 90%. Myc and p53 proteins were expressed in 20% and 10% of cells, respectively.

Cytogenetics

FISH *IRF4-DUSP22* rearranged; *JAK2* and *MYC* split probes, non-rearranged (same results in diagnostic biopsy, lymph nodes and 2025 Lyp biopsy)

Molecular Studies

TCR gamma and beta were clonal and of same size in many skin biopsies and lymph node biopsy, as well as in LyP biopsies of 2021 and 2025.

NGS: *KLF2* mutation c.248_263del p.(Pro83ArgfsTer53), VAF 23,93% in lymph node biopsy (NGS studies in 2019 diagnostic occurring and 2025 Lyp biopsy, ongoing)

Proposed Diagnosis

Primary cutaneous CD30-positive T-cell lymphoproliferative disorder, Primary cutaneous anaplastic large cell lymphoma type

Interesting Feature(s)

This is a primary cutaneous ALCL presenting a relapsing course since 2019 even Mtx and Brentuximab treatments. Clinically, an association with simultaneous LyP, particularly appearing after initiating Brentuximab, was observed. In addition, a non-described *KLF2* mutation (c.248_263del) was identified. This is an uncommon mutation mostly occurring in splenic marginal zone lymphoma. There are no functional studies in ALCL. However, the ACMG classification suggests such mutation as likely pathogenic since it is a deletion of 15 bp occurring in exon 2, probably participating in the loss of control of the NF- κ B pathway. The relapsing course of the disease underlines the need of additional therapeutic strategies for these lymphomas.

Panel Diagnosis: C-ALCL and LyP

EA4HP26-LYWS-155

Recurrent Self-Healing Papulonodular Lesions in a Young Woman: Primary Cutaneous CD30-Positive Lymphomatoid Papulosis

PhD/MD Anna Mozos¹, Malena Ferre¹, Dr. Elena Carmona², Dr. LLuis Catasús¹, Blanca Noguero¹, PhD/MD Ruth J. Orellana¹

¹ Hospital de la Santa Creu i Sant Pau, Pathology, BARCELONA, Spain; ² Hospital de la Santa Creu i Sant Pau, Dermatology, BARCELONA, Spain

Case Description

A 30-year-old woman with a clinical history dating back to 2020, when she developed a single cutaneous lesion measuring approximately 2 cm in diameter on the leg, which resolved spontaneously. Since then, she has experienced recurrent episodes of papules and nodules with spontaneous regression over a period of approximately 3 weeks.

A staging workup including PET-CT showed no pathological findings. At present, the patient presents with 4–5 violaceous papules measuring 4–5 mm in diameter, located on both arms. She denies pruritus, toxic syndrome, B symptoms, or any other associated systemic symptoms. Laboratory studies are within normal limits.

A skin biopsy of one of the active lesions was performed.

Biopsy Fixation Details

10% buffered formalin fixed and paraffin-embedded.

Frozen Tissue Available

Not-available.

Details of Microscopic Findings

Histological sections correspond to a skin biopsy showing a dense inflammatory infiltrate with a superficial perivascular and interstitial distribution. The infiltrate is composed of intermediate- to large-sized lymphocytes, some of which are binucleated or display Reed–Sternberg–like morphology.

This atypical lymphoid population is admixed with small lymphocytes and scattered eosinophils. No epidermotropism, syringotropism, or vascular involvement is identified.

Immunophenotype

Immunohistochemical studies demonstrate a CD30-positive lymphoid infiltrate, with diffuse expression of CD2 and CD4. The atypical population is negative for T-lineage markers CD3, CD5, and CD7, which are expressed only in a small subset of reactive small T lymphocytes within the infiltrate, with a density similar to that of CD8-positive cells. The proliferative index (Ki-67) is high, approximately 70%.

Cytogenetics

DUSP22 rearrangement: Not detected (FISH)

Molecular Studies

Not done

Proposed Diagnosis

Primary cutaneous CD30-positive T-cell lymphoproliferative disorder, lymphomatoid papulosis type.

Interesting Feature(s)

Lymphomatoid papulosis belongs to the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders and is characterized by a chronic, recurrent, and self-healing clinical course, despite histological features that may mimic an aggressive lymphoma.

The clinical presentation, absence of systemic involvement, histological findings with large CD30-positive cells, immunophenotype, and the self-regressing behavior of this case are characteristic of the entity.

Panel Diagnosis: LyP type A

EA4HP26-LYWS-158

Primary cutaneous epidermotropic, cytotoxic, ALK+ T-cell lymphoma

Dr. Giorgio A. Croci^{1,2}, Prof. Silvia Tabano^{1,3}, Prof. Silvia Alberti Violetti^{1,4}, Prof. Francesco Onida⁵, Prof. Emilio Berti^{1,4}

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Case Description

A 58-year old male, followed up for at least 3 years for a suspected erythrodermic psoriasis. At time of biopsy, a widespread disease was apparent, with hyperkeratotic plaques and ulcerated lesions over a poikilodermic skin. Complete staging excluded an extracutaneous disease, but the patient experienced a cutaneous progression requiring hematologic management, including gemcitabine, anti-CD30 and ALK-inhibition, with complete response, but followed by relapse and rapid, cutaneous progression, leading to death for disease.

Biopsy Fixation Details

10% buffered formalin fixed; paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

Keratotic plaque showed a lichenoid appearance, including acanthosis, hyperkeratosis and moderate spongiosis, with Civatte bodies and a moderate, band-like infiltrate in the superficial dermis, but coupled with a minor, epidermotropic population of medium to large-sized, pleomorphic cells. In the ulcerated skin, the atypical cells were partially masqueraded by granulation tissue and inflammatory cells, but a population of small-to-medium sized, atypical cells could be highlighted, with few larger cells and features of tropism to the adjacent epidermis.

Immunophenotype

Complete phenotype of the atypical cells: CD2+/-, CD3-/+ , CD5-, CD7+, CD4+ (dim), CD8-, granzymeB+, perforin+, BetaF1+, TCRdelta-, CD56-, CD45RA-, Tbet-, PD1-, EBV-EBER-. Roughly 50% of the cells demonstrated dim-to-moderate expression of CD30, with a cytoplasmic pattern of ALK-positivity (ALK1 negligible, ALK D5F3 moderate) being found on most of them, with an increasing gradient from the smaller to the largest cells.

Cytogenetics

Not performed.

Molecular Studies

TCRG rearrangement (BIOMED-2 guidelines): monoclonal.

FISH analysis: *ALK* break; RT-PCR not conclusive for low quality RNA.

Proposed Diagnosis

Epidermotropic, cytotoxic, ALK-positive cutaneous T-cell lymphoma.

Interesting Feature(s)

Our case displays a dermatological picture reminiscent of an inflammatory dermatosis, and a mycosis fungoides (MF)-like histological profile, with clinical progression to some extent overlapping primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma.

Including a further case observed at our Institution, literature search provided a total of 32 ALK+ primary cutaneous T-cell lymphoma cases, only 7 of which featuring a MF-like clinical picture (from large plaque parapsoriasis to disseminated pagetoid reticulosis-like presentation), with a longstanding course of disease over a 4-to-20 years follow up [PMID: 38780617]. Histology of MF-like cases includes a predominantly epidermotropic pattern and morphology ranging from small, atypical to pleomorphic and anaplastic cells. Tested cases featured a dim to intense CD30-expression, a CD4+/cytotoxic granule+ phenotype and either a cytoplasmic or nuclear/cytoplasmic ALK-positivity with ALK-D5F3 clone. In our 2 cases, an *ALK* break, while in one published case an *ALK::AT1C* fusion was detected. Therapeutic approach included PUVA and chemotherapy.

Experience is limited, but existent data suggest the presence of a pattern of disease, namely of primary cutaneous epidermotropic, cytotoxic, ALK-positive T-cell lymphoma. The major challenges in dealing with this subset include its prodromal phases, easily misinterpreted as inflammatory dermatosis or parapsoriasis / early phase MF. Data on its optimal management are far from being conclusive: a MF-like approach is currently chosen, but depending on CD30 and, most notably, ALK expression, a targeted therapy could be envisaged in advanced stages.

Panel Diagnosis: Aggressive lymphoma, epidermotropic, cytotoxic, ALK+

Under the eyebrow

PhD/MD Fanny Drieux¹, Dr. René Guérin², Dr. Clémence Tamarit², Dr. Alice Carricaburu³, Philippe Ruminy⁴, PhD/MD Julien Masliah-Planchon⁵, Dr. Elsa Poullot⁶, Prof. Philippe Gaulard⁶, PhD/MD Antoine Ittel⁵, Dr. Liana Veresezan¹

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Case Description

A 68-year old female, with no medical history, presented with a unique centimeter nodule under the right eyebrow. Clinically, the nodule was well-defined, reddish-pink, centered by a cluster of keratin, for which keratoacanthoma was suspected. There was no other cutaneous lesion. No extra-cutaneous localization was detected by TEP-TDM. After excision, the patient has remained well.

Biopsy Fixation Details

We received the skin excision fixed in formalin 4% and embedded in six paraffin blocks.

Frozen Tissue Available

No frozen tissue available.

Details of Microscopic Findings

Microscopic analysis showed an ulcerative and poorly differentiated dermal proliferation, of large atypical cells showing pleomorphic large nuclei, prominent nucleoli with numerous « Hallmark » cells. There was no angiocentrism, but focal necrosis.

Immunophenotype

By immunohistochemistry, the large cells presented an aberrant T-cell phenotype CD4 weak, CD3- CD5- CD2-CD7-, were positive for CD30 (strong and diffuse), CD45 (weak and heterogenous), and CD15. The tumors cells express weakly GATA3 and LEF1, while the cytotoxic markers (Tia1, perforin, granzyme b) were negative. P63 immunostaining was weak and heterogenous. The cells were also negative for CD8, CD20, ALK1, CD56, granzyme, PS100, SOX10, AE1/AE3, and there was no detection of EBER transcripts in the tumor cells.

Cytogenetics

Fluorescent in situ hybridization with the ZytoLight SPEC IRF4,DUSP22 Dual Color Break Apart Probe, showed a monoallelic rearrangement of the DUSP22/IRF4 locus.

Molecular Studies

We detected by Id-RT-PCR two alternative fusion transcripts involving *IRF4* (*LINCPINTE2a::IRF4e2* and *LINCPINTE2a::IRF4e3*). No fusion transcript involving *TP63* was detected.

Targeted gene expression profiling revealed high expression of the *TCRδ* genes, and « TH2 » markers (*CCR4* and *GATA3*), with no expression of the *HBZ* transcript of the HTLV1 virus. The phenotype γδ was further confirmed by immunohistochemistry.

The targeted sequencing performed on the FFPE biopsy (Qiaseq technology, NextSeq), using a dedicated PTCL panel targeting 60 genes, detected no somatic variant.

Proposed Diagnosis

Primary cutaneous anaplastic large cell lymphoma ALK-negative.

The hypothesis of a lymphomatoid papulosis has been ruled out by the GFELC (Groupe Français d'Etude des Lymphomes Cutanés), regarding the cytology and the clinical presentation.

Interesting Feature(s)

This is a rare case of primary cutaneous anaplastic large cell lymphoma ALK-negative with a TCR-γδ phenotype, associated with an *IRF4* rearrangement. We could detect the fusion transcript by an innovative and unusual

technology (Id-RTPCR). The $\gamma\delta$ and TH2 phenotypes were also characterized by an alternative gene expression profiling technology, further confirmed by immunohistochemistry. The significance of this phenotype is unknown, as discussed in the recent series of 11 cases (Journal of Cutaneous Pathology, 2025; 52:487–496). Unfortunately, we failed to better characterize the mutational landscape of this case, despite our extended and dedicated PTCL panel.

Panel Diagnosis: C-ALCL with DUSP22 rearrangement AND gamma/delta phenotype

EA4HP26-LYWS-162

Primary “Cutaneous” CD30-Positive T-cell Lymphoproliferative Disorder Involving the Tonsil

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Case Description

A 61-year-old man with no significant past medical history presented with two months of sore throat refractory to antibiotics. PET-computed topography demonstrated a markedly FDG-avid enlarged lingual tonsil and bilateral cervical lymphadenopathy. A lymph node biopsy revealed reactive features, which led to resection of the tonsil (reviewed below). There was no evidence of systemic disease, no splenomegaly, no skin lesions, and the CBC was normal. The patient experienced a near symptom-free indolent course over one year post-diagnosis follow-up, with decreased residual PET-avid tonsil size at four months following limited therapy with brentuximab and localized radiation.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

H&E sections of the tonsil show predominantly florid follicular lymphoid hyperplasia with focal sheets of large lymphoid cells with anaplastic morphology, including "hallmark" and "donut" forms. Atypical mitotic figures and apoptotic bodies are seen. The infiltrate demonstrates intraepithelial tumor foci reminiscent of Pautrier microabscesses/epidermotropism.

Immunophenotype

The neoplastic cells are CD2+ CD3+ CD5+ CD4+ T cells that are positive for TCR-BF1, perforin, granzyme, TIA-1, and CD30 (strong, >75%), show loss of CD7, and are negative for CD8, TCR-g, TCR-d, ALK, EBER(in situ hybridization), CD20, PAX5. The Ki67 proliferative index is >90%.

Cytogenetics

Karyotype: 46~49,XY,der(1)del(1)(p31p22)t(1;4)(q21;q31),add(7)(p2?2),der(8;13)(q10;q10), add(15)(q26),+2-4mar[cp3]/46,XY[cp12]

FISH for *DUSP22* rearrangement is pending.

Molecular Studies

Next generation sequencing (NGS) detected a high mutational burden, pathogenic mutations in *BCOR* and *TET2*, and a high number of copy number variants.

NGS-based assay for heme-related gene fusions (Archer Heme Fusion) revealed no reportable fusion transcripts, including those involving *ALK*, *TP63*, and *TYK2*.

Proposed Diagnosis

CD30-positive T-cell lymphoproliferative disorder, involving tonsil, favor primary "cutaneous" anaplastic large cell lymphoma.

Interesting Feature(s)

A rare case of a CD30+ T-cell lymphoproliferative disorder with isolated involvement of the lingual tonsil.

Remarkably focal disease in a background of florid follicular lymphoid hyperplasia resulting in striking tonsil enlargement and FDG-avid signal radiographically worrisome for aggressive disease.

While morphologically, immunophenotypically, and genetically compatible with systemic ALCL, the localized presentation and indolent course of this case is more in keeping with a primary "cutaneous" CD30+ lymphoproliferative disorder, which may rarely present in oropharyngeal mucosal sites.

This serves as an instructional example of how primary "cutaneous" forms of CD30+ lymphoproliferative disorders (primary cutaneous ALCL vs lymphomatoid papulosis, type C) should remain in the differential despite mucosal/non-cutaneous presentation.

Diagnosis is challenging and requires close clinical/radiographic correlation (demonstration of persistent or waxing and waning localized disease) for accurate diagnosis.

Highlights the need for more comprehensive comparative genetic/phenotypic studies to identify distinguishing features between systemic and primary "cutaneous" ALCL, to better inform drastically different management approaches.

Panel Diagnosis: CD30+ LPD involving tongue tonsil

EA4HP26-LYWS-169

Lymphomatoid Papulosis type E: a case report of a rare entity

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Case Description

A 41-year-old male patient without remarkable past medical history consults a dermatologist because of a painful right-sided plantar lesion. It was unclear at what moment the lesion had appeared. The patient denied any insect bites or local trauma; however, he mentioned having at least 3 past episodes of similar self-resolving skin lesions of the same localisation, with the first episode in 2021. According to the patient, no systemic clinical manifestations accompanied the skin lesion. On physical examination, a single well-demarcated 1 cm oval papule with black centre and erythematous periphery was appreciated on plantar skin of the right foot. The cutaneous punch-biopsy was performed.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded tissue.

Frozen Tissue Available

No.

Details of Microscopic Findings

The skin biopsy revealed a large transmural cutaneous necrosis with a small viable area at the level of subcutis. In occasional arterioles of deep dermis, an area of a dense intravascular and concentric perivascular mononuclear infiltrate was present. The infiltrate was composed of small to medium-sized cells showing mild to moderate atypia with some nuclei of irregular polygonal or kidney-like shape. In the vicinity of the described focus, other damaged

blood vessels surrounded by multiple nuclear debris of inflammatory cells were appreciated accompanied by foci of red blood cell extravasation. The viable subcutis demonstrated a dense mixed cellular infiltrate composed predominantly by lymphocytes without atypia, histiocytes and multiple eosinophils. Scattered atypical cells were seen.

Immunophenotype

The atypical cells within the perivascular cutaneous infiltrate intensely stained with CD3, CD2, CD5, CD8, TIA1 and CD30. BF1 and TCR delta were negative. ALK, CD56, granzyme and EBER were negative. Subcutaneous infiltrate stained positive with CD3, CD2, CD4, CD8, CD79a, CD68 and focally with CD20; scattered CD30-positive cells were detected.

Cytogenetics

Not performed.

Molecular Studies

The perivascular infiltrate underwent the T-cell receptor gene rearrangement analysis, which revealed monoclonal rearrangement of the TCRγ.

Proposed Diagnosis

Primary Cutaneous CD30-Positive T-Cell Lymphoproliferative Disorder consistent with Lymphomatoid Papulosis type E.

Interesting Feature(s)

Lymphomatoid papulosis type E is a benign self-resolving but diagnostically challenging entity that needs to be differentiated from other non-tumoral (e.g., vasculopathies) or other less indolent CD30-positive lymphoproliferative disorders that might require more aggressive treatment strategies. Clinicopathological correlation is essential in establishing a correct diagnosis.

Panel Diagnosis: LyP type E

EA4HP26-LYWS-177

Pediatric case of borderline type of primary cutaneous CD30+ lymphoproliferative disorder with *TNK1::GPS2* fusion

Dr. Mark G. Evans¹, Dr. Matthew J. Oberley¹, Dr. Sonal Choudhary², Dr. Andrew Bukowski³, Dr. Oleg E. Akilov²

¹ Caris Life Sciences, Department of Pathology, Phoenix, USA; ² University of Pittsburgh, Department of Dermatology, Pittsburgh, USA; ³ University of Pittsburgh, Department of Pediatrics, Pittsburgh, USA

Case Description

A 9-year-old boy presented with a three-year history of recurrent erythematous papules and nodules. Initial lesions were presumed to represent arthropod reactions and were treated with topical corticosteroids without sustained benefit. A biopsy of a papule on the left lower leg was interpreted as nummular eczema. Over time, the patient continued to develop intermittent pink papules that spontaneously regressed. In early 2024, he developed a solitary, rapidly enlarging nodule on the left lower abdomen accompanied by transient ipsilateral inguinal lymphadenopathy. Excision of the abdominal lesion revealed a CD30+ T-cell lymphoproliferative disorder. Comprehensive clinical staging showed no evidence of systemic involvement. Given the overall clinicopathologic findings, a diagnosis within the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders was favored. The patient was treated with low-dose oral methotrexate (5 mg weekly) with complete clinical response and remains without evidence of disease after one year of follow-up.

Biopsy Fixation Details

The abdominal excision was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The skin and subcutis demonstrate a large, ulcerated, polypoid proliferation of pleomorphic/anaplastic lymphoid cells with irregular reniform to ring-shaped nuclei. Multinucleate forms, single-cell tumor apoptosis, and numerous mitotic figures are appreciated.

Immunophenotype

The neoplastic cells are strongly CD30-positive with weak-to-moderate CD4 co-expression. They show blush-to-weak immunoreactivity for BCL2 and patchy, blush staining for CD7 and BCL6. The cells are negative for CD1a, CD34, CD5, CD8, CD20, and kappa/lambda expression. Ki-67 highlights a proliferation index approaching 100%.

Cytogenetics

Not performed.

Molecular Studies

Whole exome/whole transcriptome sequencing: *TNK1::GPS2* ex 10::ex 3 (chr17:7387457::chr17:7314597; hg38); *MAP3K1* c.835-1G>C (49% VAF).

Proposed Diagnosis

Primary cutaneous CD30+ T-cell lymphoproliferative disorder, borderline.

Interesting Feature(s)

This case highlights a rare *TNK1::GPS2* fusion, previously reported in ALK-negative anaplastic large cell lymphoma (PMID: 37400763), and structural rearrangements involving *TNK1* and *GPS2* have also been described in primary cutaneous anaplastic large cell lymphoma (PMID: 34382383). Clinically, the patient exhibited two seemingly discordant but not mutually exclusive patterns within the spectrum of primary cutaneous CD30+ lymphoproliferative disorders: intermittently recurring, spontaneously regressing papules/papulonodules (LYP-like) and a solitary, larger tumor-forming abdominal lesion that prompted excision (pcALCL-like). Given the limited number of reported *TNK1::GPS2*-positive cases across different clinical contexts, it remains unclear whether this fusion tracks with a particular phenotype or prognosis, or whether it occurs across a broader spectrum of indolent-to-tumor-forming CD30+ lymphoproliferative disorders.

Panel Diagnosis: CD30+ LPD, borderline

EA4HP26-LYWS-178

Case of primary cutaneous CD30+ lymphoproliferative disorder presenting as persistent psoriasiform plaques

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Case Description

A 79-year-old man presented with a two-year history of scaly, moderately pruritic plaques involving the upper chest, scalp, intertriginous thighs, groin, and buttocks. He was initially diagnosed with psoriasis and was treated with topical corticosteroids, followed by risankizumab for one year, without clinical improvement. Subsequent biopsies from the bilateral axillary plaques demonstrated features consistent with a primary cutaneous CD30+ lymphoproliferative disorder. The patient was monitored clinically for 12 months without the appearance of new plaques or progression to tumor-like lesions.

Biopsy Fixation Details

A right axillary skin biopsy was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Skin biopsy shows marked psoriasiform hyperplasia with intraepidermal neutrophils, along with epidermotropism and folliculotropism. The dermis demonstrates a band-like lichenoid infiltrate composed of atypical lymphocytes admixed with histiocytes, eosinophils, and neutrophils.

Immunophenotype

The atypical lymphocytes show strong expression of CD30 and CD3, with preserved CD7 expression. The CD4:CD8 ratio is not significantly altered. Ki-67 highlights a proliferation index of 20-30%. Gram, GMS, PAS, HSV, VZV, ALK, and EBER stains are unremarkable.

Cytogenetics

Not performed.

Molecular Studies

T-cell receptor gene rearrangement studies demonstrated clonality.

Proposed Diagnosis

Primary cutaneous CD30+ T-cell lymphoproliferative disorder, representing a rare clinicopathologic variant that may best be described as CD30+ psoriasiform lymphomatoid dermatitis.

Interesting Feature(s)

Psoriasiform presentations within the spectrum of primary cutaneous CD30+ lymphoproliferative disorders are rarely described. While psoriasis-like morphologies are well recognized in mycosis fungoides, particularly in psoriasiform or hyperkeratotic variants, analogous presentations in CD30+ lymphoproliferative disorders remain poorly characterized. This case illustrates a persistent, biologic-refractory psoriasiform eruption driven by a dominant epidermotropic CD30+ T-cell population, closely mimicking psoriasis both clinically and histologically. We propose that this presentation represents a distinct clinicopathologic variant best termed CD30+ psoriasiform lymphomatoid dermatitis, characterized by persistent psoriasiform plaques, neutrophilic epidermitis, and prominent CD30+ lymphocytes. Recognition of this pattern is critical to avoid prolonged misdiagnosis and inappropriate biologic therapy. Accumulation of additional cases and longer-term follow-up will be essential to clarify its relationship to other CD30+ lymphoproliferative disorders, risk of progression, and optimal management strategies.

Panel Diagnosis: Most likely MF

EA4HP26-LYWS-180

Two distinct CD30+ cutaneous lymphoproliferative disorders with T-cell differentiation arising simultaenously in a patient with history of Classic Hodgkin lymphoma

Dr. Whitney Brinkley, **Dr. Sarah DePew**

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Case Description

A 71-year-old male has a clinical history of classic Hodgkin lymphoma diagnosed in 2023 (inguinal lymph node) and was treated with chemoradiation with good response, until cutaneous relapse the following year. Additionally, in late 2024, cutaneous biopsies from an outside institution were read as "atypical T-cell infiltrate" which was CD30 positive and showed positive (clonal) T-cell receptor gene rearrangement testing by PCR, but diagnosis not otherwise specified. Approximately one year later in 2025, the patient re-presented to our institution with worsening nodular rash with large ulcerated nodule of the right axilla and multiple, smaller non-ulcerated papules of the left chest wall

and back with background erythema. Biopsies of right axilla and left superior chest wall skin were obtained which showed atypical CD30-positive lymphoproliferative neoplastic processes with two distinct clinical, morphologic, immunostaining patterns and molecular characteristics.

Biopsy Fixation Details

Formalin fixed paraffin embedded tissue

Frozen Tissue Available

Not available

Details of Microscopic Findings

A) Right axilla skin biopsy: Dermal infiltrate of atypical small-to-intermediate lymphoid cells with moderate amounts of eosinophilic cytoplasm extending deep into subcutaneous tissue. There is some epidermotropism in the overlying non-ulcerated, spongiotic epidermis. Rare background larger cells with prominent nucleoli are seen.

B) Left superior chest wall skin biopsy: Dermal infiltrate of scattered large mononucleated and binucleated cells with prominent nucleoli and a small lymphocytic/eosinophilic background. Overlying epidermis shows spongiosis.

Immunophenotype

A) Right axilla skin biopsy: Neoplastic T-cells are positive for CD3, CD30, CD4 and MUM1 (subset). They are negative for CD8, CD7, CD5, CD56, ALK, CD19, CD20, and granzyme.

B) Left superior chest wall skin biopsy: Scattered intermediate-to-large atypical cells are positive for CD30 and minor subset for CD8. They are negative for CD3, CD4, CD5, CD7, CD15, PAX5, CD20, CD45 and ALK. Background small T-cells have a decreased CD4:CD8 ratio, but are positive for CD3, CD5, and CD7.

Cytogenetics

FISH negative for DUSP22 or TP63 rearrangements

Molecular Studies

A) Right axillaskinbiopsy: Next generation sequencing detected a TP53 pathogenic mutation (VAF 64%) B) Left superior chestwall skinbiopsy: Next generation sequencing was negative for pathogenic variants

Proposed Diagnosis

A) Right axillaskinbiopsy:

-Primary cutaneous Anaplastic Large T-Cell Lymphoma (pcALCL)

-Systemic involvement cannot be entirely excluded

B) Left superior chest wall skin biopsy:

-CD30+ lymphoproliferative disorder, not otherwise specified

-Differential diagnosis includes cutaneous CD30 positive T-cell neoplasm with loss of most markers of T-cell differentiation (lymphomatoid papulosis or pcALCL), involvement by systemic CD30 positive T-cell neoplasm, or relapsed classic Hodgkin lymphoma

Interesting Feature(s)

- This case highlights the spectrum of CD30+ cutaneous lymphoproliferative disorders, which can show different backgrounds, immunohistochemical staining patterns and molecular characteristics in different lesions occurring simultaneously

- Overlapping features of CD30+ T-cell lymphomas and classic Hodgkin lymphoma such as Hodgkin-Reed Sternberg-like cells and similar immunostaining profiles can make final diagnosis challenging, especially in cutaneous sites

- TP53 mutations can occur in primary cutaneous anaplastic large T-cell lymphoma and are associated with a non-indolent clinical course

Panel Diagnosis: Most likely C-ALCL. Relation to previous cHL unclear and diagnosis cHL unconfirmed

CD30+ anaplastic large cell lymphoma with rare *TNK1::GPS2* fusion

Dr. Mark G. Evans¹, Dr. Anthony Crymes², Dr. Matthew J. Oberley¹, Dr. Mark Boonyasampant³

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Case Description

A 56-year-old man was hospitalized for heart failure exacerbation with weakness and shortness of breath. Computed tomography was performed to rule out pulmonary embolism and demonstrated multiple body wall masses, corresponding to firm cutaneous nodules that had developed during the previous six months; by report, some may have resolved spontaneously, and they were nontender and thought to be related to recent medication changes. Bilateral lung nodules were also seen on imaging, in addition to a T6 vertebral mass, bilateral iliac and inguinal lymphadenopathy, and a 6.7-cm enhancement of the right psoas muscle. A biopsy was performed on the psoas lesion, which was diagnosed as ALK-negative anaplastic large cell lymphoma. Shortly after biopsy, the patient succumbed to his widespread malignancy.

Biopsy Fixation Details

The right thigh biopsy was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The biopsied fibroconnective tissue demonstrates a dense infiltrate of atypical lymphoid cells with increased nuclear:cytoplasmic ratio; pleomorphic/anaplastic nuclei are appreciated, including lobated and multinucleated forms. Occasional wreath-like cells and focal necrosis are noted.

Immunophenotype

The atypical lymphocytes show expression of CD30, CD43, CD45, EMA, and CD99. They do not demonstrate staining for CD3 or ALK. CD20 and PAX5 highlight scattered small B cells.

Cytogenetics

Not performed.

Molecular Studies

Whole exome/whole transcriptome sequencing: *TNK1::GPS2* ex 10::ex 3 (chr17:7387457::chr17:7314597; hg38); *TP53* p.H179Y (19% VAF).

Proposed Diagnosis

ALK-negative anaplastic large cell lymphoma, primary cutaneous versus systemic disease involving the skin.

Interesting Feature(s)

The *TNK1::GPS2* fusion has been rarely reported in ALK-negative anaplastic large cell lymphoma (PMID: 37400763). Clinically, the distinction between primary cutaneous anaplastic large cell lymphoma and systemic lymphoma involving the skin is difficult to determine in this case. The cutaneous lesions may have developed early in the clinical presentation, and some may have spontaneously regressed and recurred. However, given the extent of tumor and its aggressive behavior, ultimately resulting in the patient's demise, a non-skin origin is possible. Moreover, the disease course might suggest that poor prognosis is associated with the presence of the *TNK1::GPS2* fusion; however, similar *TNK1* and *GPS2* gene rearrangements have also been documented in primary cutaneous anaplastic large cell lymphoma (PMID: 34382383) with more favorable outcomes. The prognostic significance of this rare intergenic fusion warrants further investigation as additional cases are documented in the future.

Panel Diagnosis: Systemic ALCL with secondary skin involvement

Post-Therapeutic Phenotypic Alteration in Primary Cutaneous Anaplastic Large Cell Lymphoma: Decreased CD30 Expression and Deep Soft Tissue Extension Mimicking Peripheral T-Cell Lymphoma

Dr. Maikel Benitez Barzaga, Dr. Catalina Amador-Ortiz, [Dr. Xiaoqiong Wang](#)

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Case Description

- A 61-year-old man presented with a complaint of a progressively worsening “psoriasis” plaque on the right foot.
- He has a history of cutaneous lymphoma diagnosed at an outside institution five years earlier as CD30-positive mycosis fungoides versus primary cutaneous anaplastic large cell lymphoma. He was treated with brentuximab, with a good clinical and radiographic response.
- Physical examination showed an ulcerated mass-like lesion extensively involving the dorsal and plantar aspects of the foot.
- HTLV serology test was negative. PET/CT showed a multinodular, infiltrative soft tissue lesion encompassing the underlying osseous structures and involving nearly the entirety of the right foot, with a maximum SUV of 18.9. No significant lymphadenopathy or visceral organ involvement was identified.
- Right foot amputation was performed.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

H&E sections show diffuse involvement by a lymphoma, extending from ulcerated skin into the deep fibroconnective tissue. Focal involvement of bone and bone marrow is also identified. Geographic necrosis and increased vascularity are present. The lymphoma cells shows diffuse growth pattern and are composed of intermediate- to large-sized oval to polygonal cells with irregular to convoluted nuclei, occasional prominent nucleoli, and abundant cytoplasm. Focally, the tumor cells display a sarcomatoid appearance, with short spindle cells arranged in a strand-like growth pattern. Prominent perivascular accentuation of lymphoma cells is also present. Occasional eosinophils are identified.

Immunophenotype

The lymphoma cells are positive for CD3, CD2, CD4 (subset, dim), CD30 (subset, dim), TIA and granzyme B, and are negative for CD5, CD7, CD8, ALK, and TCR gamma. EBV in situ hybridization stain is negative.

Cytogenetics

ALCL FISH is positive for gains of ALK and DUSP22/IRF4, and is negative for ALK, TP63 and DUSP22/IRF4 rearrangement

Molecular Studies

Foundation Heme NGS panel identified multiple pathogenic mutations and gene amplifications, including two pathogenic TP53 mutations.

Proposed Diagnosis

CD30+ T cell lymphoma, favor primary cutaneous anaplastic large cell lymphoma

Interesting Feature(s)

- We report a case of relapsed primary cutaneous ALCL with deep soft tissue involvement, followed by subsequent systemic progression.
- The lymphoma cells show focal sarcomatoid morphology.
- Although CD30 expression is not diffuse in this post-therapeutic specimen, the morphologic features and cytotoxic immunophenotype support the diagnosis of anaplastic large cell lymphoma and help distinguish it from other

cutaneous T-cell lymphomas.

•FISH and NGS showed multiple genetic alterations, in keeping with its aggressive clinical behavior.

Panel Diagnosis: C-ALCL, relapsed

EA4HP26-LYWS-198

Lymphomatoid Papulosis with 5' Deletion of *DUSP22-IRF4* and Gamma-Delta T-Cell Phenotype: A Rarity

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Case Description

An 81-year-old male with Alzheimer dementia presented with a single ulcerated 6 mm skin nodule on his back in 10/2009. He had no palpable lymphadenopathy (LAP), no hepatosplenomegaly, no B symptoms, normal CBC, & normal serum LDH level. Excised lesion was sent to pathology department in 10% NBF. "Bread-loafing" it showed "fish-flesh"-like, soft, cut surfaces, & it was embedded in paraffin. ALK-negative cutaneous anaplastic large cell lymphoma (cALCL) was diagnosed. Bone marrow aspirate & biopsy did not show any significant abnormality. Whole-body CT, PET/CT, & MRI revealed no LAP or mass lesion. Radiotherapy was given only to the excision site. No chemotherapy was given. MRI & PET/CT scans remained normal & no additional skin lesion, LAP or mass appeared till last follow-up in 2011.

Biopsy Fixation Details

10% Neutral Buffered Formaldehyde

Frozen Tissue Available

Not available

Details of Microscopic Findings

H&E sections show ulcerated epidermis, prurient scale crust & a diffuse band-like, upper dermal, infiltrate of medium-sized lymphoid cells with high NC ratio, mildly condensed chromatin & small prominent nucleoli. Many mitoses are present. A small number of small lymphocytes are present under the lesion. Non-ulcerated epidermis shows only a few bland-looking small lymphocytes in it.

Immunophenotype

Immunohistochemistry: Medium-sized lymphoid cells are +ve for CD45, CD2, CD3, CD30, MUM1, MYC, LEF1 (~40%), TCRD, and Ki67 (~90%), and are negative for CD20, CD79a, CD4, CD8, CD5, CD7, ALK-1, TCRBF1, GATA3, TBX21, CD10, CD15, CD56, TIA-1 (~5%), granzyme B (~5%), perforin (~5%), BCL1, BCL2, BCL6, TdT, & EBV-LMP1. CD138 shows only rare plasma cells. The small number of small lymphocytes in the epidermis surrounding the lesion were CD30 negative (*i.e.* no biphasic pattern).

Cytogenetics

Conventional cytogenetics was not done,

Molecular Studies

In situ Hybridization: EBER is negative.

T Cell Clonality Studies (PCR): TCR beta & TCR gamma rearrangements detected

Break-apart (BAP) FISH: 5' deletion of *DUSP22-IRF4* in 58% nuclei

Dual Color- Dual Fusion FISH for t(6;7)(p25.3;q32.3): Negative

DNA/RNA NGS: Low-level mutations in *CHECK2*, *CCNE1*, *RAD50*, *ATM*, *SMARCA4*, *PPM1D*, *KMT2D* genes; T cell clonality detected (TRDV2/TRGV10); increased MYC mRNA reflecting promoter hijacking; no 5' deletion *DUSP22-IRF4* or *DUSP22* gene fusion with any other gene (probable RNA degradation in old tissue)

Proposed Diagnosis

Y Lymphomatoid Papulosis with 5' Deletion of *DUSP22-IRF4* and Gamma-Delta T-Cell Phenotype

Interesting Feature(s)

1. **$\gamma\delta$ type lymphomatoid papulosis ($\gamma\delta$ -LyP):** It is a rarity which, unlike other $\gamma\delta$ T cell lymphomas, is indolent & is likely to be misdiagnosed as ALK-negative cALCL (*Am J Surg Pathol.* 2024;48:501-510; *JEADV Clinical Practice*, 2025;4:883-6; <https://doi.org/10.1111/cup.70009>). Our case was initially diagnosed as ALK-negative cALCL.
2. **5' *DUSP22-IRF4* deletion in $\gamma\delta$ LyP:** No t(6;7)(p25.3;q32,3) rearrangement found by D-FISH but *DUSP22-IRF4*-R with a non-7q partner cannot be excluded. *DUSP22-IRF4*-R is known to occur in LyP but its detection in $\gamma\delta$ -LyP has only recently been reported in 2 case reports (<https://doi.org/10.1111/cup.70009>; *Am J Dermatopathol.* 2023;45:831-4).
3. **Equivocal LEF1/TIA-1 immunophenotype:** This equivocal immunophenotype goes along with equivocal *DUSP22*-R status (*Am J Surg Pathol.* 2022;46:1490-9; *Human Pathol.* 2024;150:58-66).
4. **Mutational Profile of $\gamma\delta$ LyP with 5' *DUSP22-IRF4* deletion:** Our case is the first documentation of mutational profile of $\gamma\delta$ LyP with 5' *DUSP22-IRF4* deletion &, therefore, adds to previously known information (*JID Innovations* 2022;2:100068; *JID Innovations* 2021;2:100034).

Panel Diagnosis: spectrum/borderline or C-ALCL

EA4HP26-LYWS-206

Multifocal primary cutaneous anaplastic large cell lymphoma (cALCL) with *DUSP22* rearrangement & p63 upregulation

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Case Description

32 year old lady presented in 2022 with 2 months' history of multiple skin lumps on the trunk & bilateral upper & lower limbs, the largest a 17cm fungating left shin nodule with central ulceration. This enlarged to 26cm over a month prior to treatment. CT showed prominent bilateral axillary, inguinal lymph nodes (LNs) & non-specific pulmonary ground-glass nodules. PET disclosed multiple FDG-avid cutaneous lesions & inguinal LNs suspicious for disease. The patient was given methotrexate & radiotherapy to the limbs, with reduction in size & metabolic activity of the irradiated lesions. The non-irradiated lesions however progressed, & new FDG-avid nodules developed in the lungs & skin. The patient was then given brentuximab & CHP (B-CHP) with resolution of the skin lesions. The hypermetabolic inguinal LNs gradually subsided & the lung nodules remained stable without metabolic activity. At latest follow up (Nov 2025), 32 months post-B-CHP, there were no skin lesions & no PET evidence of recurrence.

Biopsy Fixation Details

Neutral buffered formalin, 24-48 hours

Frozen Tissue Available

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Details of Microscopic Findings

Incisional biopsy of a left flank skin nodule showed sheets of large lymphoid cells with irregular (including horseshoe, wreath-like) nuclei, prominent nucleoli, infiltrating the dermis & subcutis, with foci of intralymphatic permeation. Numerous mitoses, including atypical forms, & epidermal ulceration were noted. No epidermotropism or angioinvasion was seen.

A left inguinal 'lymph node' was excised a month later at another institution, which turned out to be a dermal-subcutaneous nodule of essentially similar pathology. No lymph node was identified.

Immunophenotype

The lymphomatous large cells diffusely express CD30, LCA, CD43, MUM1, p63 & BCL2, are focally BCL6+, weakly & focally CD7+, & negative for other T cell (CD3, CD2, CD5, CD4, CD8, TCR-BF1, TCR-delta), cytotoxic (TIA1, Granzyme B), TFH (CD10, PD1, ICOS, CXCL13), B cell (CD20, CD79a, PAX5), macrophage (MPO, CD163, CD68) markers, ALK, CD56, CD138, TdT, CD34, CD117, CD123, CD1a, S100, EMA, AE1/3 & EBER-ISH. The Ki67 proliferation index is 60-80%.

Cytogenetics

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Molecular Studies

Interphase FISH using breakapart probes to DUSP22 at 6p25.3 showed disruption in 92.5% of 200 nuclei.

Proposed Diagnosis

Primary cutaneous anaplastic large cell lymphoma (cALCL)

Interesting Feature(s)

The diagnosis of cALCL requires clinical correlation to exclude other differentials of CD30+ T cell LPD, namely lymphomatoid papulosis (LyP), cutaneous involvement by systemic ALK-ALCL & transformed mycosis fungoides (MF). Her clinical history was not typical of LyP & MF.

Nodal involvement was never confirmed histologically as the excised inguinal 'LN' turned out to be a cutaneous nodule of ALCL. The lack of extracutaneous involvement thus made cALCL more likely than skin involvement by ALK-ALCL.

Despite the apparently aggressive initial presentation of multiple skin lesions on the trunk, bilateral upper & lower limbs with regional lymphadenopathy (by PET) & possible extracutaneous (lung) disease, the patient responded well to systemic B-CHP & has remained recurrence-free for 32 months. This suggests the p63 IHC upregulation may not correlate with TP63 rearrangement by FISH, which typically portends a poor prognosis & aggressive, often treatment-refractory behaviour. Unfortunately TP63-FISH was not available at the time of workup.

Panel Diagnosis: C-ALCL

EA4HP26-LYWS-219

Inflammatory Soil: Lymphomatoid Papulosis type E and Mycosis fungoides preceding Classic Hodgkin Lymphoma in a 30-year-old patient.

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Case Description

A 30-year-old male patient with a clinical history of lymphomatoid papulosis (LyP) type E diagnosed in 2013 (at age 19) and Mycosis fungoides (MF) diagnosed in 2017. Since diagnosis, the patient has exhibited LyP lesions in skin (submitted 1) and oral mucosa, characterized by spontaneous regression, alongside MF patches (subm 2) managed with corticosteroids.

The patient currently presents with cervical lymphadenopathy, in the absence of systemic symptoms. Clinical and PET-CT staging reveals cervical and inguinal lymphadenopathy (Stage III). An excisional biopsy of the cervical lymph node (LN) was taken (subm 3).

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The skin lesion (LyP) showed ulceration, and an infiltration of the dermis with angiocentricity.

The skin lesion (MF) presented well-developed foci of lymphocytes within the epidermis.

The LN (CHL) architecture was preserved, showing partial effacement due to an irregular expansion of the mantle zone. The interfollicular area remained intact. Within this area of expansion, there was a prominent presence of large atypical cells with Hodgkin or RS morphology, accompanied by small lymphocytes, eosinophils, and focal fibroblastic proliferation.

Immunophenotype

The LyP cells were positive for CD3, CD2, CD5, CD4, CD30 and TIA-1. ALK1 negative.

The MF showed positivity for CD3, CD2, CD5 and CD4. CD30 negative.

In the LN (CHL), the atypical cells were positive for PAX5 (weak), MUM1, CD30 and CD15. CD20, CD79a, CD3, CD4 and EBV (EBERs and LMP1) were negative. The lymphocytes around the atypical cells were positive for T-cell markers. PD1 showed scattered positive cells.

The interfollicular lymphoid cells were positive for T-cell markers without antigen losses.

Cytogenetics

Not performed

Molecular Studies

T-cell receptor (TR) gamma clonality analysis studies were polyclonal. Previous LyP and MF lesions were monoclonal with identical peaks

Proposed Diagnosis

Classic Hodgkin Lymphoma (CHL) in a Young Adult with a history of LyP type E and MF.

Interesting Feature(s)

The coexistence of LyP, MF and CHL in a single patient remains exceptionally rare and has been reported almost exclusively as isolated case reports. While Molgó et al. described this triad in an older adult, our patient is a young adult, indicating that the biological events driving multi-lineage lymphomagenesis can occur much earlier in life than suggested by prior literature. This challenges the conventional understanding that such complex lymphoproliferative associations primarily affect older populations.

Large series demonstrate that patients with MF and patients with LyP carry a significantly increased risk of second malignancies, particularly hematologic neoplasms. Studies of LyP show associated hematologic malignancies in roughly 15-20% of patients, most often MF, primary cutaneous ALCL and CHL. Probably chronic antigenic stimulation, a cytokine-rich inflammatory milieu, and prolonged immune dysregulation may create a permissive environment for independent malignant transformation.

In patients with established LyP/MF who develop lymphadenopathy, there is a strong temptation to interpret nodal enlargement as dermatopathic lymphadenitis, nodal involvement by MF or CD30+ large cell transformation. The partial lymph node involvement by CHL in this case, combined with the patient's complex lymphoproliferative history, underscore the critical importance of excisional lymph node biopsy. Core biopsies carry substantial risk of misclassification, and excisional lymph node biopsy remains the recommended standard for definitive diagnosis.

Panel Diagnosis: LyP type E and mycosis fungoides preceding cHL

Primary cutaneous anaplastic large cell lymphoma with the regional lymph node dissemination after the electron radiation treatment in an 11-year-old male

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Case Description

An 11-year-old, previously healthy male presented with two growing skin lesions for 3-4 weeks: one lesion was on the right side of nose overlying the ala - circular, well circumscribed skin colored to slightly waxy appearing papule about 0.5-1.0 cm in diameter; the other one was a similar, 0.5cm and less raised lesion a few centimeter away on the right cheek. The right cheek lesion was biopsied and consistent with primary cutaneous anaplastic large cell lymphoma (C-ALCL). The skin lesions was resolved after the electron radiation treatment for four month. Two month later, he developed an enlarging solitary lymph node in the right submandibular region, which was PET-avid. He had no constitutional symptoms or new skin lesions. The lymph node biopsy was performed.

Biopsy Fixation Details

The specimens of skin biopsy and lymph node excisional biopsy were received separately in fresh; subsequently fixed in 10% buffered formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the skin biopsy show a diffuse and dense atypical lymphoid infiltrate in the dermis. The monotonous lymphoid population shows small to moderate sized cells with open chromatin, mildly irregular nuclear contours, occasional nucleoli and scant cytoplasm. Scattered mitotic figures are seen. There is no granuloma, epidermotropism or angiocentric infiltrate.

Sections of the lymph node show architectural effacement by diffuse neoplastic lymphoid proliferation. There are scattered, clusters or sheets of large neoplastic cells with pleomorphic nuclei, multiple nucleoli, and abundant amphophilic cytoplasm. Occasional multinucleated neoplastic cells and hallmark cells with eccentrically placed large horseshoe-shaped nuclei are evident. Mitotic figures are frequently noted. The background of mixed small lymphocytes and histiocytes cells are present.

Immunophenotype

Immunostains on the skin biopsy show the neoplastic cells are positive for CD3, CD30, and negative for ALK-1, TdT, CD34, CD20, CD56, CD68, S-100, CD1a and EBER.

Flow cytometry performed on the lymph node in a reference lab reported no immunophenotypic abnormality detected.

Immunostains on the lymph node show the neoplastic cells are positive for CD3 (dim), CD2, CD5, CD8, CD30, CD15, TIA-1, Granzyme B, MUM-1, LEF1 and negative for CD4, CD7, ALK-1, EMA, CD20, Pax5 and EBER.

Cytogenetics

FISH analysis on lymph node showed no evidence for DUSP22-IRF4, TP63 and TBL1XR1/TP63 rearrangements.

Molecular Studies

TRG PCR on the skin biopsy showed clonal T-cell receptor gene rearrangement.

Proposed Diagnosis

1. Skin lesion:
 - Consistent with primary cutaneous anaplastic large cell Lymphoma, ALK-negative
2. Lymph node:
 - Anaplastic large cell lymphoma, ALK-negative

Interesting Feature(s)

- The patient presented with multiple skin lesions which can be seen in about 20% of patients.
- The skin lesions responded to the electron radiation treatment; but months later the patient developed ALCL extracutaneous dissemination in the regional lymph node that occurs in approximately 10% of cases.
- Although a definitive distinction between C-ALCL and lymphomatoid papulosis cannot be certain at diagnosis; a definitive diagnosis of C-ALCL or lymphomatoid papulosis may be evident on clinical follow-up.
- The primary C-ALCL of this case demonstrated the feature of small cell morphology but C-ALCL disseminated in the lymph node demonstrated the feature of large, pleomorphic cells with anaplastic morphology.
- CD3 expression was weak in the lymph node but strong in the skin lesion.

Panel Diagnosis: C-ALCL

EA4HP26-LYWS-239

CD30-positive primary cutaneous lymphoproliferative disorder, CD30-negative

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Case Description

74-year-old male, receiving a diagnosis of early phase mycosis fungoides (MF) in 2008 (biopsy not available for review). Since 2013, papules with central erosion, mostly featuring a remitting / relapsing behavior over the years (last relapse in 2025), but some requiring local radiotherapy, some, on the face, biopsied to rule out basal cell carcinoma (biopsy submitted). Currently, no clinical lesions typical of MF. Staging ruled out extracutaneous disease.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Along all biopsies from 2013 to 2025 (2024 specimen submitted), acanthosis and erosion, in presence, in the underlying dermis, of a dense, cellular infiltrate, with polymorphic composition. The proliferative fraction consists of small-to-medium sized, slightly pleomorphic cells, filling the epidermis and follicular structures in a pagetoid reticulosis-like fashion. At the periphery, a heavy inflammatory population is observed, including polymorphic T-cells and abundant small B-cells and plasma cells.

Immunophenotype

Complete phenotype: CD2-, CD3+, CD5-, CD7+/-, CD30-, CD4-, CD8+/- (dim), CD56-, TIA1+, granzymeB-, PD1-, CD45RA-, EBV/EBER-. "TCR-silent" (BetaF1-/TCRdelta-)

Cytogenetics

Not performed

Molecular Studies

TCRG rearrangement (BIOMED-2 guidelines): monoclonal, with comparable peaks (electropherograms available for 2021, 2024 and 2025 biopsies).

IGH+IGK rearrangement (BIOMED-2 guidelines): polyclonal (2024 biopsy)

Proposed Diagnosis

Epidermotropic, TCR-silent, cytotoxic, T-cell lymphoproliferative disorder, clinically consistent with lymphomatoid papulosis.

Interesting Feature(s)

Shared morphologic and phenotypic profiles hamper the histologic differential diagnosis among primary cutaneous, epidermotropic, cytotoxic T-cell lymphomas (TCL), which may be prompted only by adequate clinical correlation, but, most importantly, follow up. This includes cytotoxic MF, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic TCL (AECTCL), gamma/delta TCL, extranodal NK/T-cell lymphoma, and lymphomatoid papulosis (LyP), particularly type D. Although CD30 expression is a defining feature of classic LyP, a subset of cases, most often within the type D variant, demonstrate minimal, focal, or entirely absent CD30 staining (PMID: 30520526). This lack of CD30 reactivity voids a key diagnostic feature and increases the risk of misclassification as more aggressive epidermotropic cytotoxic TCL.

The BetaF1-/TCRdelta- (TCR silent) phenotype was considered in line with proper CD30-positive T-cell lymphomas / lymphoproliferative disorders (LPD), both nodal and extranodal, which share a heavily disrupted canonical T-cell differentiation and signaling program (PMID: 20511667). This feature, also observed in hepatosplenic and enteropathy-associated TCL (PMID: 21753698), in the proper context supports a diagnosis of CD30+ LPD.

Challenging features of the presented case include the past history deemed consistent with MF, though not confirmed by lack of original biopsy, nor of typical clinical lesions at follow up, and the histologic picture closely mimicking AECTCL. However, its distinctive clinical pattern was regarded supportive, in the words of dr. Macaulay, of “Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign--histologically malignant” (PMID 5634442). CD30- LyP represents a diagnostically problematic subset within the spectrum of primary cutaneous CD30+LPD. Also, it stresses the need to regard the diagnosis of primary cutaneous LPD as a matter of clinic-pathologic pattern, rather than adherence to strict criteria.

Panel Diagnosis: LyP type D, CD30 negative

EA4HP26-LYWS-244

A case of cutaneous CD30-positive lymphoproliferative disorder

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Case Description

- 30 year old male patient
- No comorbidities or addictions
- Skin rash on right chest wall and axilla since 6 years, accompanying axillary lymphadenopathy since 3 years

Biopsy Fixation Details

10% neutral buffered formalin for 6 hours

Frozen Tissue Available

Not available

Details of Microscopic Findings

Skin biopsy from axilla:

- Skin covered tissue with a nodular superficial dermal, periadnexal as well as perivascular infiltrate of atypical large lymphoid cells accompanied by small lymphocytes, eosinophils and histiocytes.
- The larger atypical lymphoid cells show anaplastic morphology.
- No epidermotropism

Immunophenotype

Positive stains:

- CD4, CD8 (CD4 expression is weaker and lesser than CD8), CD30, GATA3, CD71, CD25, TIA1

Negative stains:

- CD20, PAX5, CD15, EMA, CD79a, CD3, CD7, ALK1, EBERish

Cytogenetics

Not available

Molecular Studies

Not available

Proposed Diagnosis

- Primary cutaneous CD30 +ve lymphoproliferative disorder, favouring:
 - Primary cutaneous anaplastic large cell lymphoma (pcALCL), ALK-negative

Interesting Feature(s)

- The histology (diffuse CD30 in large pleomorphic cells, hallmark cells) + presence of a large nodular lesion that is persistent fits diagnostic features of pcALCL.
- 6-year chronicity might at first suggest LyP (which is classically chronic and long-standing). But LyP typically demonstrates multiple, recurrent lesions that spontaneously regress. The current lesion is a persistent large nodule — this clinical behavior favors pcALCL.
- Regional nodal enlargement (bulky axillary node) can occur with pcALCL and does not automatically mean systemic ALCL. Locoregional nodal involvement may still carry a good prognosis for pcALCL but changes management.
- The CD8-predominant phenotype of the large cells is an uncommon but reported variant of pcALCL and does not preclude the diagnosis; such cases are often indolent but require clinical correlation and follow-up.

Panel Diagnosis: C-ALCL

EA4HP26-LYWS-263

Primary mucosal CD30+ T-cell lymphoma with striking T-cell reactive population

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Case Description

A 54-year-old woman with a CHEK1 germline mutation, celiac disease, a systemic autoimmune disorder with pulmonary involvement, and sicca syndrome without Sjögren's criteria, was diagnosed with a localized **ALK-negative anaplastic lymphoma of the nasal mucosa** with locoregional lymphadenopathy. A BMB was performed and did not show lymphoma infiltration. She was treated with brentuximab and CHPx6 followed by ASCT (2020-2021), achieving sustained complete remission.

She subsequently developed recurrent infectious complications and autoimmune flare-ups, with identification of a **reactive oligoclonal T-cell population** in peripheral blood (2023), retrospectively detected in biopsies since 2018 (skin, liver, intestinal, and bone marrow) sharing identical TCR oligoclonal peaks. PET imaging was unremarkable.

The clinical picture was classified as a secondary hyperinflammatory syndrome due to suspected T-cell dysregulation—associated immunodeficiency with multisystem involvement, refractory to treatment, and the patient died in 2025; autopsy is ongoing.

Biopsy Fixation Details

Formalin-Fixed Paraffin-Embedded.

Frozen Tissue Available

No.

Details of Microscopic Findings

- Nasal mucosa tumoral sample (2020):

Diffuse infiltration by a proliferation of large anaplastic-appearing cells, with extensive necrosis.

The cells exhibit large, lobulated nuclei with prominent nucleoli and abundant cytoplasm.

Occasional hallmark cells are identified.

Immunophenotype

- Nasal mucosa tumoral sample (2020) by IHC:

Tumor cells are weakly positive for CD3 with loss of CD5 and CD7, and partial expression of CD4; CD8 is negative. CD30 is positive in 95% of cells, a subset of cells expresses Granzyme B and TIA-I, and p63 is positive in some large cells. EMA, ALK and EBER are negative.

-Blood sample (2023) by flow cytometry:

Atypical T-cell population

+ CD3 cytoplasmic, CD2, CD7, CD11c, CD45RA, CD94 heterogeneous (20%), perforin, Granzyme B

- CD3 Surface, CD5, CD4, CD8, CD16, CD57, CD45RO, CD197, CD27, CD25, HLA-DR, TCLL-1, CD30, CD10, CD279, CD57, CD28, TRBC1 (completely negative, monotypic)

Cytogenetics

-Nasal mucosa tumoral sample (2020):

FISH *TP63* BA and *IRF4/DUSP22* BA normal.

Molecular Studies

-Blood sample (2023) and the remaining biopsies analyzed retrospectively:

PCR TCR (gamma): oligoclonal with the same peaks in all samples.

Proposed Diagnosis

- Anaplastic Large Cell Lymphoma (ALCL), ALK-negative/Mucosal CD30-positive T-cell lymphoproliferation
- Oligoclonal T-cell reactive population

Interesting Feature(s)

On one hand, this represents a primary CD30-positive mucosal lymphoproliferation/ALK-negative ALCL mucosal lymphoma. Mucosal CD30-positive T-cell lymphoproliferative disorders are rare and show clinical overlap with cutaneous CD30-positive T-cell lymphoproliferative disorders.

Accurate classification of primary cutaneous/mucosal ALCL requires appropriate clinical staging. Primary forms have a favorable prognosis, and overtreatment should be avoided.

Because of its rarity this entity is difficult to categorize.

On the other hand, there is a striking persistence of an oligoclonal T-cell population associated with a fatal hyperinflammatory syndrome.

Panel Diagnosis: ALK negative mucosal CD30+ T-LPD/ALCL

DUSP22-rearranged primary cutaneous CD30-positive T-cell lymphoproliferative disorder

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Case Description

A 59-year-old woman with a history of actinic keratosis and dysplastic nevi presented with an erythematous skin lesion on the upper left breast that had been present for one to two months. Her family history was notable for breast cancer in her maternal grandmother and colon cancer in her paternal grandfather. Physical examination revealed firm, dome-shaped, pink cutaneous nodules on the midline of the upper left breast. The remainder of the skin examination was unremarkable, with no additional patches or plaques identified. The clinical differential diagnosis included an atypical nevus versus basal cell carcinoma. A shave biopsy of the cutaneous nodules was performed. The specimen consisted of a skin shave biopsy measuring 1.2 × 1.0 × 0.2 cm.

Biopsy Fixation Details

The biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 5 µm thickness, and stained with hematoxylin and eosin.

Frozen Tissue Available

Not applicable.

Details of Microscopic Findings

Microscopic examination revealed a biphasic growth pattern. A dense dermal infiltrate composed of large pleomorphic lymphocytes was present. These atypical lymphocytes exhibited slightly basophilic cytoplasm, large irregular nuclei with coarse heterochromatin along the nuclear membranes, and subset prominent nucleoli. Scattered mitotic figures were identified within the dermal infiltrate. In addition, a pagetoid reticulis-like pattern of epidermal infiltration by small, irregular, hyperchromatic lymphocytes was observed, with prominent tagging of the small lymphocytes along the basal epidermal/dermal junction.

Immunophenotype

Immunohistochemical analysis was performed using a Ventana Benchmark instrument (Ventana, Tucson, AZ). Immunophenotypic analysis demonstrated that the neoplastic cells were positive for CD2, CD3, CD30 and LEF1. The neoplastic cells were negative for ALK1, CD4, CD5, CD7, CD8, EMA, PAX5, p63 and TIA1.

Cytogenetics

Fluorescence in situ hybridization (FISH) for anaplastic large cell lymphoma was performed on formalin-fixed, paraffin-embedded tissue using probes for ALK (Abbott Vysis), TP63, TBL1XR1/TP63, and DUSP22-IRF4 (Agilent SureFISH). Slides were processed per standard protocols, with nuclear counterstaining using 4',6-diamidino-2-phenylindole (DAPI). A DUSP22-IRF4 rearrangement at 6p25.3 was detected in 70% of analyzed nuclei. The other probes showed normal/negative results.

Molecular Studies

Not performed.

Proposed Diagnosis

These findings are consistent with a DUSP22-rearranged (DUSP22-R), CD30-positive T-cell lymphoproliferative disorder, with a differential including DUSP22-R lymphomatoid papulosis (LyP) versus ALK-negative anaplastic large cell lymphoma (ALCL) with DUSP22-R. Distinction between these entities requires clinical correlation and systemic evaluation. Our patient had persistence and growth of the breast lesion post biopsy, with occurrence of a second lesion neighboring the original site. PET scan revealed no evidence of systemic disease. Given the clinical and imaging findings, the patient was diagnosed with primary cutaneous anaplastic large cell lymphoma (C-ALCL). At the time of this submission, the patient has undergone 2 radiation treatments.

Interesting Feature(s)

LyP with DUSP22-R is rare, and presentation as a solitary nodule is unusual. Clinically distinguishing LyP from C-ALCL or systemic ALCL with secondary cutaneous involvement is important, as ALCL is more clinically aggressive, often requiring radiation therapy or chemotherapy in systemic cases. Both LyP and C-ALCL with DUSP22-R can show a biphasic growth pattern as seen in this case.

Panel Diagnosis: DUSP22 rearranged C-ALCL

EA4HP26-LYWS-272

Primary Cutaneous Intravascular/Intralymphatic CD30-Positive T-Cell Lymphoproliferative Disorder with *DUSP22* Translocation

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Case Description

81 year-old female with a history of facial rash for 6 months, asymptomatic. It improved with topical steroids but then new lesions showed up. The patient had a history of mantle cell lymphoma, on maintenance therapy (rituxan), and also history of breast cancer 20 years prior, treated with chemotherapy and endocrine therapy.

A skin punch biopsy was taken from the right temple. PET CT scan y bone marrow biopsy were negative.

The patient passed away 14 months after diagnosis, due to unrelated pulmonary embolism.

Biopsy Fixation Details

Formalin-fixed paraffin embedded tissue

Frozen Tissue Available

No

Details of Microscopic Findings

Sections show large atypical cells within dermal lymphatic vessels. Telangiectasia is also present.

Immunophenotype

The intralymphatic atypical cells are positive for CD4, CD30, and MUM1 while negative for CD3, CD7, and CD8.

Only a subset of tumor cells are positive for TCR betaF1 and TIA-1, while the tumor cells are negative for TCRdelta and ALK.

D2-40 highlights the vessels involved by the lesion.

Cytogenetics

POSITIVE RESULT FOR IRF4/DUSP22 REARRANGEMENT.

nuc ish(IRF4/DUSP22x2)(5'IRF4/DUSP22 sep 3'IRF4/DUSP22x1)[149/200]

Interpretation:

200 cells have been analyzed, 74.5% of cells show IRF4/DUPS22 rearrangement

Molecular Studies

Clonality studies by high throughput sequencing showed *TRG* monoclonal rearrangements; studies were negative for *TRB* rearrangements.

Proposed Diagnosis

Cutaneous Intralymphatic ALK-negative Anaplastic Large Cell Lymphoma/CD30-positive Lymphoprolifeative Disorder with *DUSP22* translocation

Interesting Feature(s)

Very rare case of cutaneous intravascular/intralymphatic CD30-positive T-cell lymphoproliferative disorder, with demonstrated *DUSP22* translocation, ALK-negative

Indolent presentation with erythematous lesion, asymptomatic

No history of systemic or nodal CD30-positive T-cell lymphoid proliferation or lymphoma

It highlights unusual presentations of cutaneous CD30-positive T-cell lymphoproliferative disorders and diagnostic utility of FISH and immunohistochemistry

Recognition of this entity is essential to avoid misclassification as aggressive lymphoma and to guide appropriate management.

This case expands the clinicopathologic spectrum of CD30-positive T-cell LPD and emphasizes the importance of integrating morphologic, immunophenotypic, and genetic data in rare cutaneous lymphoid proliferations.

Panel Diagnosis: Primary cutaneous intravascular/intralymphatic CD30-positive T-LPD with DUSP22 rearrangement

EA4HP26-LYWS-283

The $\gamma\delta$ Dilemma: Distinguishing Transformed Mycosis Fungoides From Primary Cutaneous $\gamma\delta$ T-Cell Lymphoma

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Case Description

A 60-year-old female with a history of diabetes mellitus, hypertension, peripheral vascular disease, and a recent cerebrovascular accident (CVA; left pontine, early 2025) with residual right-sided weakness, presented with a refractory, progressive right lower extremity wound. Initially managed as an infected diabetic foot ulcer (MSSA/Enterococcus positive), the lesion proved recalcitrant to debridement and hyperbaric oxygen therapy, eventually necessitating a right below-knee amputation (BKA). A biopsy of the site 12 months prior showed only dermal fibrosis and chronic inflammation without evidence of a neoplastic process. Parallel to the limb lesion, the patient developed multifocal, painful, and pruritic erythematous patches on the bilateral hands, palms, axillae, and anterior thigh. These lesions were refractory to antifungals and were initially dismissed as decubitus ulcers or neuropathy secondary to her CVA.

Biopsy Fixation Details

Representative skin and soft tissue from the BKA specimen were fixed in 10% neutral buffered formalin and processed for routine histology.

Frozen Tissue Available

Not performed.

Details of Microscopic Findings

Sections reveal an ulcerated epidermis with a dense, sheet-like atypical lymphoid infiltrate involving the papillary and deep dermis. The neoplastic cells are large with irregular nuclear contours, vesicular chromatin, and prominent nucleoli. Mitotic activity and apoptotic bodies are frequent.

Immunophenotype

The neoplastic infiltrate is CD3+ with a CD4-/CD8-phenotype. There is a partial loss of CD5, most pronounced in the superficial neoplastic cells. TCR $\gamma\delta$ is positive, confirming a $\gamma\delta$ T-cell phenotype. The cytotoxic profile shows partial perforin expression but is negative for TIA-1, granzyme B, and CD56. A subset of neoplastic cells is CD30+. CD20, CD10, BCL6, and EBER ISH are negative.

Cytogenetics

Not performed.

Molecular Studies

Next-generation sequencing demonstrated loss of CDKN2A and CDKN2B, as well as a pathogenic JAK3 mutation (c.4724T>C; p.A573V)

Proposed Diagnosis

Primary cutaneous T-cell lymphoma, $\gamma\delta$ phenotype, with features overlapping between Mycosis Fungoides (Large-Cell Transformation) and Primary Cutaneous $\gamma\delta$ T-cell Lymphoma.

Interesting Feature(s)

This case demonstrates the diagnostic challenge in dealing with T-cell neoplasms of $\gamma\delta$ phenotype. While the two-year indolent patch–plaque evolution with the lack of systemic symptoms suggests MF, the subsequent aggressive ulceronecrotic lesion, $\gamma\delta$ TCR phenotype, and molecular profile (JAK3 p.A573V, *CDKN2A/B* loss) raise the possibility of PCGDTCL versus large-cell transformation of MF. Immunophenotypically, CD3⁺/CD4[−]/CD8[−]/CD5[−] cells with incomplete cytotoxic marker expression (perforin⁺/TIA-1[−]/GrB[−]/CD56[−]) further obscure diagnostic clarity. A prior nondiagnostic biopsy and clinical confounders (neuropathy, fungal infection) delayed diagnosis. This mismatched MF-like course, but PCGDTCL-like behavior, remains a diagnostic dilemma. Mutational similarities in JAK/STAT pathways, KRAS, and EZH2 suggest shared mechanisms of oncogenesis in these two entities. Approximately 10% of MF cases display a $\gamma\delta$ T-cell receptor phenotype. Although $\gamma\delta$ MF is typically indolent, up to 37% of cases may progress to a PCGDTCL-like phenotype with aggressive clinical behavior. The disease exists on a biologic spectrum; therefore, classification must evolve to accommodate genomic and phenotypic fluidity.

Panel Diagnosis: Primary cutaneous T-cell lymphoma with overlapping features between MF and primary cutaneous gamma/delta T-cell lymphoma

EA4HP26-LYWS-286

CD30(+) T-cell lymphoproliferative disorder presenting as nodular lesions of the cheek

Dr. Tran B. Nguyen¹, Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

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Case Description

The patient is a 70-year-old man with a history of hypogammaglobulinemia who presented with skin nodules of the right lower cheek. He underwent a punch biopsy of the cheek lesion. Following the final diagnosis, he received six cycles of BV-CHP chemotherapy. At the most recent follow-up, there was no evidence of disease progression.

Biopsy Fixation Details

Sections of the skin biopsy were fixed in formalin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

The skin biopsy shows a diffuse dermal infiltrate of large mononuclear cells with prominent nucleoli and brisk mitotic activity. The epidermis is uninvolved.

Immunophenotype

The infiltrate was composed of large atypical cells that were positive for CD3 and CD30; and negative for CD4, CD5, CD7, CD8, CD20, CD25, ALK-1, CD56, TIA-1, and Granzyme B. EBER in-situ hybridization is negative.

Cytogenetics

FISH DUSP22 **positive** for rearrangement of the DUSP22 gene region. FISH TP63 is negative.

Molecular Studies

Not performed.

Proposed Diagnosis

CD30(+) T-cell lymphoproliferative disorder, favor primary cutaneous ALK-negative anaplastic large cell lymphoma, DUSP22-rearranged.

Interesting Feature(s)

- The localized cutaneous presentation, characteristic dermal-based morphology, CD30-positive/ALK-negative immunophenotype, and the presence of a DUSP22 rearrangement support the diagnosis of primary cutaneous ALK-negative anaplastic large cell lymphoma, DUSP22-rearranged.
- DUSP22 rearrangement is associated with a distinct molecular subgroup and, in the cutaneous setting, is generally linked to a favorable prognosis. TP63 rearrangements are associated with aggressive clinical behavior, advanced-stage disease, and poor outcomes in ALK-negative ALCL.

Panel Diagnosis: CD30 positive T-LPD / C-ALCL with DUSP22 rearrangement

EA4HP26-LYWS-290

CD30+ T cell lymphoproliferative disorder

Sarang Khan, Reenal Patel, Olabisi Afolayan-Oloye

Corewell Health William Beaumont University Hospital, Pathology, Royal Oak, USA

Case Description

An 81-year-old woman with a history of epidermotropic T-cell lymphoma (diagnosed at an outside facility in 2022 from a right abdominal skin punch biopsy). Histologic sections showed psoriasiform epidermal hyperplasia with a brisk band-like lymphocytic infiltrate. Numerous small-to-medium lymphocytes were present within the epidermis, with parakeratosis containing neutrophils and epidermotropic lymphocytes. Immunohistochemistry showed the lymphocytes were positive for CD3, CD30 (~70%), and BetaF1, and negative for CD2, CD4, CD5, CD7, CD8, TIA-1, Granzyme B, CD56, TCR delta, and CD20. A T-cell receptor gene rearrangement assay demonstrated a dominant clonal T-cell population. Overall findings supported cutaneous T-cell lymphoma. Loss of multiple T-cell antigens was unusual for mycosis fungoides, though a double-negative (CD4-/CD8-) variant has been reported. The patient now reported unintentional weight loss for which she underwent an extensive 18F-FDG PET scan at our hospital, which demonstrated FDG-avid lymphadenopathy involving the bilateral supraclavicular regions, right axilla, retroperitoneum, right iliac, and right inguinal regions. The maximum standardized uptake value (SUV) was 12.8, prompting tissue biopsy.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

N/A

Details of Microscopic Findings

Hematoxylin and eosin (H&E)-stained sections reveal sheets of large atypical mononuclear and multinucleated cells with prominent eosinophilic nucleoli. These are set within a mixed inflammatory background composed of small lymphocytes, numerous eosinophils, plasma cells, neutrophils, and histiocytes. Mummified cells are present, and mitotic figures are noted.

Immunophenotype

Positive markers: CD2, CD4, CD30, CD43, Clusterin, EMA

Negative markers: CD3, CD20, ALK, CD15, PAX5 CD5, CD7, CD8, CD45, Granzyme, EBER.

Cytogenetics

Negative for IRF4 and DUSP22 gene rearrangements by FISH

ISCN: nuc ish(IRF4,DUSP22)x2)[200]

Molecular Studies

Monoclonal T-cell receptor-gamma (TCR-gamma) gene rearrangement identified

TCR-gamma 1: **Prominent monoclonal peak identified (size 205 bp black)**

TCR-gamma 2: Polyclonal pattern

TCR-gamma V1: **Prominent monoclonal peaks identified (size 232 and 242 bp)**

TCR-gamma V2: Polyclonal pattern

TCR-gamma V3: Polyclonal pattern

TCR-gamma V4: **Prominent monoclonal peak identified (size 162 bp)**

Proposed Diagnosis

Overall morphology and Immunophenotype supports a CD30 positive T-cell lymphoproliferative disorder/lymphoma, ALK-negative.

Differentials would include ALK-negative primary cutaneous anaplastic large cell lymphoma or ALK-negative systemic anaplastic large-cell lymphoma and transformed mycosis fungoides.

CD30 positive lymphoproliferative disorder, favor transformed mycosis fungoides

Interesting Feature(s)

This case illustrates an unusual progression of cutaneous T-cell lymphoma to a transformed phenotype with histologic features mimicking anaplastic large-cell lymphoma. The presence of large atypical mononuclear and multinucleated cells with prominent eosinophilic nucleoli, abundant eosinophilic infiltrate, and mummified cells is striking. Immunophenotypically, the tumor was CD30-positive and ALK-negative, raising a challenging differential diagnosis between ALK-negative systemic anaplastic large-cell lymphoma, primary cutaneous ALCL, and transformed mycosis fungoides. The final diagnosis of transformed mycosis fungoides was favoured and supported by the negative DUSP22 FISH studies, emphasizing the importance of integrating morphology, immunophenotype, and molecular studies in distinguishing these entities.

Panel Diagnosis: Concordant, most likely transformed MF although not proven

EA4HP26-LYWS-297

ALK(+) anaplastic large cell lymphoma with a primary cutaneous presentation

Dr. Tran B. Nguyen¹, Dr. Eric D. Carlsen^{1,2}, **Dr. Luis F. Carrillo**¹

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Case Description

The patient is a 60-year-old woman with a history of chronic lymphocytic leukemia/small lymphocytic lymphoma who initially presented with subcutaneous nodules in the left upper arm and underwent a skin biopsy. Two years later, she developed right inguinal lymphadenopathy, which was initially suspected to represent involvement by CLL/SLL; however, biopsy demonstrated involvement by ALK-positive anaplastic large cell lymphoma. Following the final diagnosis, she underwent bone marrow transplantation. At the most recent follow-up, there was evidence of recurrent disease involving the lumbar spine.

Biopsy Fixation Details

Skin and lymph node specimens were fixed in formalin.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Skin: Sections show a deep subcutaneous infiltrate composed of large cells with irregular nuclear contours, stippled chromatin, distinct nucleoli, and moderate amounts of cytoplasm.

Lymph node: Smears show large atypical cells with irregular nuclear contours, irregularly clumped chromatin, prominent nucleoli, and fine cytoplasmic vacuoles. The needle cores demonstrate a dense infiltrate of large transformed cells with cleared to vesicular chromatin, prominent nucleoli, and moderately abundant pale eosinophilic cytoplasm. Some larger lymphoid cells show "horseshoe" or "hallmark" morphology. Some small mature lymphoid cells are interspersed. Scattered apoptotic cells are also noted.

Immunophenotype

Skin: The large neoplastic cells are positive for CD30, ALK-1; and negative for CD3, CD5, and CD20.

Lymph node: The neoplastic cells are positive for CD30, ALK-1, BCL-6(scattered), MUM1, cMYC; and negative for CD3, BCL-2, PAX-5, and CD10.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

ALK(+) anaplastic large cell lymphoma with a primary cutaneous presentation

Interesting Feature(s)

- ALK-positive ALCL most commonly presents as a systemic lymphoma involving lymph nodes and extranodal sites, whereas primary cutaneous involvement is rare and typically associated with ALK-negative disease. The initial manifestation as subcutaneous nodules raises the possibility that the cutaneous lesion represented an early or extranodal presentation of systemic ALK-positive ALCL, highlighting a rare and diagnostically challenging clinical scenario.
- Although ALK-positive ALCL generally carries a more favorable prognosis compared with ALK-negative disease, particularly in younger patients, this case demonstrates disease recurrence involving the lumbar spine following bone marrow transplantation, indicating an aggressive clinical course. Relapsed disease after transplant is associated with a poor prognosis and limited therapeutic options.

Panel Diagnosis: Systemic ALK-positive ALCL with subcutaneous presentation

EA4HP26-LYWS-319

The CD30-positive cutaneous lesion: Anaplastic large cell lymphoma / indeterminate dendritic cell tumor.

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Case Description

55yo female presented with 2 month history of chronic abscess located beneath the left breast. No similar lesions were observed elsewhere on the body, no prior history of comparable skin lesions, no known comorbidities. An excisional biopsy of the cutaneous lesion was consistent with primary cutaneous CD30+ T-cell lymphoproliferative disorders and the most consistent in the differentials was primary cutaneous anaplastic large cell

lymphoma(ALCL).An insect bite reaction was considered as a less likely.At six-month follow-up without any treatment, a persistent 3cm nodule was noted at the same site and was subsequently excised. PETrevealed no evidence of systemic lesions. Laboratory parameters were normal.In the second biopsy, the CD30+atypical large-cell componentwas observed only focally. For this reason, additional immunohistochemical studies were performed on the first biopsy

Biopsy Fixation Details

%10formalin

Frozen Tissue Available

no

Details of Microscopic Findings

First biopsy:The epidermis showed parakeratosis and acanthosis with intraepidermal eosinophils,neutrophils,lymphocytes.Focal ulceration was present.A wedge-shaped infiltrate composed of abundant eosinophils,neutrophils,lymphocytes,histiocytes together with atypical large cells Neutrophilic microabscess formation was observed.

Second biopsy:In the dermis,a predominantly perivascular infiltrate with a tendency to form coarse nodular aggregates was composed bunch of large cells accompanied by numerous lymphocytes,histiocytes,eosinophils.

Immunophenotype

First biopsy:atypical cells were

CD30(>95%),CD45,CD43,Fascin **positive**,CD20,CD3,CD2,CD5,CD7,CD4,CD8, ALK,CD21,CD23,CD34,CD68,CD 163,,SOX10,S100 **negative**. There were CD1a+/ langerin-Langerhans cells, scattered CD123+ plasmacytoid dendritic cells.ki67was approximately 80%.

Second biopsy:The large atypical cells were CD30+,EMA-,ALK-T and B cell markers negative. Patchy CD68- and CD163-positive histiocytes were present in the background, some of which were also positive for Fascin.Ki-67 was positive in a small subset of CD30-positive cells (<10%).

Cytogenetics

not done

Molecular Studies

EBER(ISH)-

Proposed Diagnosis

ALK- Anaplastic Large Cell Lymphoma,null phenotype/Indeterminate dendritic cell tumor

Interesting Feature(s)

When the findings from both biopsies were evaluated together, the differential diagnosis included CD30-positive lymphoproliferative disorders (with ALCL as the leading consideration), Langerhans cell histiocytosis, dendritic cell neoplasms, and CD30-positive reactive conditions such as an insect bite reaction.

Clinically, despite a lesion duration exceeding six months, regression of CD30-positive atypical cells was observed in the new biopsy. In conjunction with the immunophenotype of these cells (CD1a positive, langerin negative), these findings favored the possibility of an indeterminate dendritic cell tumor. However, based on the current findings, ALK-negative ALCL with a null-cell phenotype could not be definitively excluded.

Panel Diagnosis: C-ALCL with dendritic cell component, not classifiable

Recurrent *DUSP22-IRF4* rearranged lymphomatoid papulosis

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Case Description

56-yrs old female, otherwise healthy, with 1 cm large skin nodule at the left side of the thorax. She already underwent excisional biopsy of the 1 cm skin tumor of upper back 12 years previously; the diagnosis of primary cutaneous ALCL was established in outside institution. After the first biopsy, staging procedures have been performed with bone marrow biopsy which turned out to be negative. She was not treated by any therapy but was closely clinically followed up. During the period of 12 years (between first and second excision), she has been experiencing relapses of smaller, redish, spontaneously disappearing nodular changes on the skin of the neck and both upper arms. Current clinical examination again showed few papulonodular changes measuring up to 5 mm on the skin of both arms. Otherwise, clinical examination was unremarkable as well as laboratory results. Bone marrow biopsy was negative. PET CT didn't show increased uptake anywhere in the body.

Biopsy Fixation Details

10% buffered formalin overnight

Frozen Tissue Available

No

Details of Microscopic Findings

H&E of the first biopsy with LEF-1 immunostaining is provided as well as H&E with LEF-1, CD3, CD8, CD30 of current, second biopsy. There is a nodular dermal infiltrate consisting of medium sized atypical lymphatic cells with oval to cerebriform nuclei, vesicular chromatin and inconspicuous cytoplasm. Focal epidermotropism could be seen.

Immunophenotype

Positive for CD30, CD3, CD8, LEF-1, negative for CD4, CD5, CD20, ALK. There is a focal epidermotropism with biphasic pattern of CD30 expression: epidermotropic cells are weakly CD30+ while dermal show strong CD30 expression.

Cytogenetics

DUSP22-IRF4 rearrangement by FISH in both biopsies.

Molecular Studies

NA

Proposed Diagnosis

WHO HAEM5/ICC2022: *DUSP22-IRF4* rearranged lymphomatoid papulosis (LyP), recidivant after 12 years of primary diagnosis

Interesting Feature(s)

LyP with *DUSP22-IRF4* rearrangement is a rare subtype of LyP. *DUSP22* gene rearrangements are recurrent in systemic and cutaneous ALK-negative anaplastic large cell lymphomas, rarely encountered in other cutaneous CD30+ lymphoproliferations, and typically absent in other peripheral T-cell lymphomas. LyP with *DUSP22-IRF4* rearrangement shows an indolent clinical behaviour, with frequent spontaneous regression of untreated lesions. The benign clinical course despite pathologic features mimicking an aggressive lymphoma emphasizes the importance of clinicopathologic correlation. It is important to recognize this rare variant to avoid misclassification, which could lead to unnecessarily aggressive patient management. Based on prior reports, it appears that LyP with *DUSP22-IRF4* rearrangement consistently affects older individuals (aged 60 years and older), with a male predilection which was not a case in our patient. Our patient is a female being 44-yrs old at the time of initial diagnosis; that widens the clinical spectrum of this rare entity.

Panel Diagnosis: Concordant, albeit moved in spectrum

Granulomatous and eccrinotropic lymphomatoid papulosis

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Case Description

A 60-year-old male patient, with no available remote medical history. Slides in consultation on a biopsy of a lesion clinically described as a “nodular, squamous lesions involving the lower limbs and the trunk”, receiving a histological diagnosis of “granulomatous dermatitis, most likely granuloma annulare”.

After picking up the phone, the following clinical picture is provided: multiple papules since 6 months, asymptomatic, waxing and waning, with no response to steroid. Not taking any drug. No clinical-laboratoristic evidence of infectious nor systemic disease, no known immune deficiency (HCV+ hepatitis several years earlier, currently with negative RNA). Referred to local Dermatology Unit, where 2 further biopsies are taken.

Therapy: low dose methotrexate, achieving complete remission (follow up: 4.5 yrs)

Biopsy Fixation Details

10% buffered formalin fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Consultation biopsy (no block available) provided a granulomatous picture, with multinucleated, Langan-type giant cells, forming ill-defined, non-necrotizing granulomas and associated with a polymorphic, mostly lymphocytic infiltrate. Interestingly, the process appeared to be enhanced along eccrine glands, where scattered, large cells, at times with pyknotic nucleus (“mummified”) could be seen

Further biopsies reveal a V-shaped, dermal, lymphoid infiltrate, with variable amount of blastic to anaplastic cells, mostly in perivascular distribution, but also with peri-eccrine accentuation, where scattered “mummified” cells are still appreciated

Immunophenotype

Consultation biopsy: mostly mature T-cells, with unremarkable phenotype (CD2+, CD3+, CD5+; reactive-type CD7 modulation on CD4+ lymphocytes, fully preserved on CD8+). Large/atypical cells: CD30+dim/MUM1+

Further biopsies: CD30+(moderate to intense)/CD4+/MUM1+ on larger cells, with clearcut defective T-phenotype (CD2+/-, CD3+, CD5-, CD7-)

Cytogenetics

Not performed

Molecular Studies

TCRG rearrangement (BIOMED-2 guidelines): monoclonal, with comparable peaks among all biopsies.

Proposed Diagnosis

Lymphomatoid papulosis, with eccrinotropic and granulomatous features

Interesting Feature(s)

Lymphomatoid papulosis (LyP) encompasses a spectrum of histologic variants, unified by the paradoxical combination of histologic malignancy and clinically indolent behavior. Beyond the classic subtypes, several rare morphologic variants pose additional diagnostic challenges.

These include forms with eccrinotropism, which up to date have been seldomly described and usually carries granulomatous features [PMID 12760293]. The presence of granulomatous inflammation, often with epithelioid histiocytes or multinucleated giant cells admixed with atypical, (possibly) CD30+ lymphoid cells, introduces another

layer of complexity. This pattern may resemble inflammatory / reactive granulomatous dermatitis, infectious processes, or even cutaneous involvement by systemic lymphomas. In the setting of CD30+ lymphoproliferative disorders, it likely represents a late lesion, prodromal to its complete healing.

Key features of the present case include the identification, mostly in vicinity to eccrine glands, of scattered, large, convoluted cells, to some extent resembling mummified elements, dimly highlighted by CD30 and more clearly by MUM1, the latter being a sensitive marker of lymphocyte activation in LyP, thus proving the diagnostic value morphology in pathology. Also, clonality analysis did not make a diagnosis, but it supported the histologic suspicion, which could be confirmed upon careful clinical assessment and sampling of diagnostically meaningful, full blown LyP lesions.

Panel Diagnosis: Granulomatous and eccrinotropic LyP

EA4HP26-LYWS-367

Hodgkin-Like Transformation in Mycosis Fungoides? A Composite Lymphoma in Question

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¹ University Hospital Essen, Institute of Pathology, Essen, Germany; ² University Hospital Essen, Department of Dermatology, Essen, Germany

Case Description

We report a case of a 68-year-old male patient with a history of classical Hodgkin lymphoma diagnosed in 2023 and a subsequent diagnosis of mycosis fungoides in 2024. While undergoing treatment for mycosis fungoides, the patient developed an enlarged inguinal lymph node in the region of affected skin. The skin biopsy demonstrated histopathologic features consistent with mycosis fungoides, whereas the lymph node revealed features consistent with classical Hodgkin lymphoma.

Biopsy Fixation Details

0,9 x 0,7 x 0,4 cm skin biopsy. 2,2 x 1,4 x 1 cm lymph node, fixed in 4,5 % buffered formalin for 8-16 hours (over night). Time to fixation <5 minutes.

Frozen Tissue Available

No frozen tissue available.

Details of Microscopic Findings

Inguinal skin lesions showed band-like infiltrates of lymphoid cells accompanied by few eosinophils and 'lined up' enlarged lymphoid cells within the junctional zone.

The inguinal lymph node featured infiltrates of large, blastoid cells with Hodgkin-Reed-Sternberg-like morphology accompanied by a sheet-like infiltrate of monomorphic, small lymphocytes and eosinophils.

Immunophenotype

Lymphocyte infiltrates within the inguinal skin were CD3, CD4 and partially CD30 positive and CD8, CD15, CD20, CCL17/TARC and CCL22/MDC negative.

HRS-like cells within the inguinal lymph node expressed CD30, CD15, CCL17/TARC, CCL22/MDC and were negative for EBV, PAX5, Granzyme B and TIA-1.

Cytogenetics

Cytogenetic studies were not performed.

Molecular Studies

Molecular assessment of IgH and TCR could not identify monoclonal rearrangements.

Next generation sequencing revealed identical mutations of DNTM3A within the skin, lymph node and peripheral blood of the patient (c.2618A>G p.His873Arg).

PCR and sanger sequencing of microdissected HRS-like cells and lymphocytes of the inguinal lymph node did not show any DNTM3A mutation.

Proposed Diagnosis

Mycosis fungoides with Hodgkin-like involvement of draining lymph node or Composite lymphoma of mycosis fungoides and classical Hodgkin lymphoma

Interesting Feature(s)

Question of true composite lymphoma or Hodgkin-mimicking mycosis fungoides with an apparent switch in morphology and differentiation (CCL22/MDC and CLL17/TARC only positive within the lymph node). Immunophenotype of classical Hodgkin lymphoma (CD15, CD30, CCL22/MDC, CCL17/TARC positive) but PAX5 and EBV negative. Polyclonal TCR and IgH in lymph node tissue. Matching DNTM3A Mutation in skin biopsy, lymph node and peripheral blood, but not DNTM3A Mutation in microdissected HRS-like cells or lymphocytes.

Panel Diagnosis: MF transformation to Hodgkin-like proliferation

EA4HP26-LYWS-374

Cutaneous Anaplastic Large Cell Lymphoma Presenting with Involvement of Nasal Sidewall and Ala

Dr. Samer Z. AlQuran¹, Dr. Mohamed Hegazi², Dr. Victor G. Prieto³, Dr. Alexander Marchak¹, PhD/MD student Abdurrahman S. AlQuran⁴, Dr. Mustafa Al-Kawaaz¹

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Case Description

A 54-year-old man with a history of CHF, hypertension, and hyperlipidemia developed a progressively enlarging left nasal mass first identified on CT scan of sinuses, which showed marked soft tissue fullness of the left nasal sidewall/ala, and to lesser degree of the columella with marked narrowing of the left nasal orifice, paranasal sinus mucosal thickening and no bony erosion. The patient reported decreased sense of smell and occasional bloody nasal discharge, without vision changes or swallowing difficulty. No other lesions were present. Initial skin biopsy was reported as benign; however, the lesion continued to increase in size. Repeat biopsy performed after a month demonstrated involvement by a CD30-positive lymphoproliferative disorder, with a differential diagnosis including anaplastic large T-cell lymphoma. CT scan of chest with contrast showed scattered paratracheal and hilar lymph nodes likely reactive, and nonspecific bilateral axillary lymph nodes likely reactive. The patient has since been treated with brentuximab vedotin and localized radiation therapy.

Biopsy Fixation Details

10% Neutral Buffered Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Examination of histologic section revealed an abnormal dense lymphoid infiltrate, mostly involving the deep dermis. The infiltrate is composed of large atypical lymphoid cells admixed with small-to-medium-sized lymphocytes, neutrophils, and eosinophils. There is only focal epidermotropism by the small-to-medium-sized lymphocytes. The large pleomorphic cells have large round and oval nuclei with small to prominent nucleoli. They include occasional binucleated forms with occasional hallmark cells.

Immunophenotype

Immunohistochemical studies show that the large neoplastic lymphoid cells are positive for CD30, CD4 (variable), CD43, CD45, MUM1, TIA1 and perforin with high labeling of nuclei by Ki-67 and focal weak immunoreactivity for CD2 and CD56. The neoplastic cells were negative for CD3, CD5, CD7, CD8, ALK1, LEF1, STAT3, CAM5.1 and pan CK. There are scattered small T and B cells. CD20 and PAX5 highlight background B-cells. ISH for EBER was negative.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

CD30 positive T-cell lymphoproliferative disorder, favor anaplastic large cell lymphoma.

Interesting Feature(s)

Involvement of nasal wall clinically mimicking NK/T-cell lymphoma. Dim expression of CD56

Panel Diagnosis: C-ALCL

EA4HP26-LYWS-401

Primary cutaneous anaplastic large cell lymphoma presenting as an elbow cyst

Dr. Amer Wahed, **Dr. Brenda Mai**, Dr. Andy Nguyen, Dr. Jacob Armstrong, Dr. Phuoc Nguyen, Dr. Kurt Jugo, Dr. Paul Chaiken

University of Texas Health Science Center Houston, Pathology, Houston, USA

Case Description

83-year-old female with persistent erythematous cystic swelling of the right elbow.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

None available

Details of Microscopic Findings

- Sheets of monomorphic atypical large cells that are infiltrating the dermis and arranged cohesively around the vessels
- The cells have atypical blastoid nuclei with moderate eosinophilic cytoplasm

Immunophenotype

CD4 (variable), CD30, Granzyme (subset), TIA1 (Subset), LEF1 are positive
CD8, ALK, TCR-beta, TCR-delta, STAT3, EBER ISH are negative

Cytogenetics

Not performed

Molecular Studies

DUSP22-IRF4 deletion (42% of nuclei)

Proposed Diagnosis

Primary cutaneous anaplastic large cell lymphoma, CD30-positive, ALK-negative

Interesting Feature(s)

- Primary Cutaneous Anaplastic Large Cell Lymphoma (PC-ALCL) is a type of T-cell lymphoma that starts in the skin; it is characterized by large CD30-positive cells, usually appearing as reddish-brown bumps or nodules that can ulcerate, and generally has a good prognosis with a high survival rate, though recurrence is common and

requires monitoring for spread to lymph nodes or other organs.

•The presentation for this case is unusual in that primary cutaneous ALCL typically presents as a rapidly growing nodule or plaque and not a cystic structure, as seen in this patient.

Panel Diagnosis: C-ALCL

EA4HP26-LYWS-405

Lymphomatoid Papulosis

Dr. Kurt A. Jugo, Dr. Andrew Cook, Dr. Phuoc Christie-Nguyen, Dr. Sahib Kalra, Dr. Jacob Huddin, Dr. Amer Wahed, Dr. Andy Nguyen, Dr. Jacob Armstrong, Dr. Brenda Mai

University of Texas Health Science Center Houston, Pathology and Laboratory Medicine, Houston, USA

Case Description

36-year-old female with multiple lesions on the left forearm.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

Not performed

Details of Microscopic Findings

Sheets of monomorphic atypical large cells infiltrating around the collagen in the dermis

Immunophenotype

Positive: CD4, CD30, Granzyme B, TIA1

Negative: CD8, ALK, LEF1, TCR-beta, TCR-delta, STAT3, EBER ISH

Cytogenetics

Not performed

Molecular Studies

DUSP22-IRF4 gain (24% of nuclei)

Proposed Diagnosis

Lymphomatoid papulosis

Interesting Feature(s)

- Lymphomatoid papulosis (LyP) with DUSP22-IRF4 rearrangement is a rare (<15 cases reported), recently described variant of LyP
- Histopathologically characterized by a biphasic growth pattern with epidermotropic small-to-medium-sized atypical T-cells and dermal large and transformed T-cells diffusely expressing CD30; interestingly our case did not have a biphasic pattern and had a wide list of differential diagnoses
- LyP with DUSP22-IRF4 rearrangement can mimic other cutaneous lymphoproliferative disorders, particularly primary cutaneous anaplastic large cell lymphoma (pcALCL) or transformed mycosis fungoides (MF)
- Unlike pcALCL or transformed MF, LyP with DUSP22-IRF4 rearrangement shows an indolent clinical behavior, with frequent spontaneous regression of untreated lesions.
- Thus, it is important to recognize this rare variant of LyP to avoid misclassification, which may potentially lead to unnecessarily aggressive patient management

Panel Diagnosis: Concordant, type C, if clinical context fits

Composite lymphoma consisting of a) primary cutaneous CD30+ lymphoproliferative disorder; b) marginal zone lymphoma

Dr. Kyriakos Orfanidis, Prof. George Rassidakis

Karolinska University Hospital, Department of Pathology and Cytology, Solna, Stockholm, Sweden

Case Description

- 78-year-old man with a ca 10-15-year hx of clinically presumed psoriasis and a one-year course of evolving cutaneous lesions
- In spring 2024 he developed a papule on the upper arm that progressed to a large ulcerated lesion (6x6 cm) with an adjacent plaque (3x3 cm); additional lesions later appeared at other sites (including lower extremity).
- Multiple skin biopsies in 2024 showed atypical lymphoid infiltrates with variable architecture (predominantly dermal in ulcerated lesions, and epidermotropic in plaque/macular lesions) and an unusual immunophenotype, prompting multidisciplinary lymphoma conference review and extended staging work-up including bone marrow studies that demonstrated a small clonal B-cell population.
- After local radiotherapy to the larger ulcerated lesion, he developed several new thin erythematous plaques. A new 4-mm punch biopsy was taken from an erythematous plaque on medial right thigh.

Biopsy Fixation Details

Routine formalin-fixed, paraffin-embedded (FFPE) punch biopsy (4 mm).

Frozen Tissue Available

Not available.

Details of Microscopic Findings

- Acanthotic, spongiotic epidermis with prominent epidermotropism of lymphoid cells extending into the upper epidermis. Surface changes include compact orthokeratosis with areas of confluent parakeratosis, focal neutrophilic debris and serous exudate.
- The dermis (to mid reticular dermis) shows mild-moderate superficial perivascular/periadnexal lymphoid infiltrates with scattered neutrophils
- No deep dermal/subcutaneous component.
- PAS-diastase is negative for fungal structures and shows no basement membrane thickening.

Immunophenotype

- Dense epidermotropic infiltrate of small-medium CD3+ T cells, CD2 preserved with reduced CD5 and CD7
- Cytotoxic phenotype CD8>CD4
- CD30+ cells constitute the majority
- PD-1+, CXCL13-, Granzyme B-, CD10-, CD15-, ALK1-, BCL6-, CD43+, TCRβ+, LEF1-. Ki-67 ca 75%
- Dermal infiltrates show the same phenotype
- Small B-cell aggregates: CD20+, CD79a+, PAX5+, CD23-, CD10-, BCL6-

Cytogenetics

FISH for DUSP22 rearrangement negative.

Molecular Studies

- PCR: clonal IGK, TCRG and TCRB
- Gamma matches prior biopsies (2024), while some beta products differ, consistent with persistence of the T-cell clone with minor beta variability.
- Overall, findings support concomitant clonal B-cell and T-cell populations across serial biopsies.

Proposed Diagnosis

Composite lymphoma consisting of:

1. primary cutaneous CD30+lymphoproliferative disorder;

2. marginal zone lymphoma

Interesting Feature(s)

An unusual CD30+ CD8-predominant epidermotropic T-cell proliferation mimicking MF/dermatitis, occurring in a patient with proven concurrent MZL and persistent dual (TCR and IGK) clonality across multiple biopsies, with DUSP22-negative status.

Panel Diagnosis: No definitive diagnosis of CD30+ T-LPD/C-ALCL. Rather, MF or other epidermotropic T-cell lymphoma are also very possible

EA4HP26-LYWS-423

Primary cutaneous anaplastic large cell lymphoma presenting as a painful left calf mass

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Case Description

82-year-old male with a painful left posterior calf mass.

Biopsy Fixation Details

Biopsy fixation involves 10% neutral buffered formalin (NBF).

Frozen Tissue Available

No

Details of Microscopic Findings

- Histological sections show sheets of monomorphic atypical large cells with blastoid chromatin and variably cherry red macronucleoli
- Mitotic figures are abundant

Immunophenotype

Positive: CD4, CD30, Granzyme (subset), LEF1

Negative: CD8, ALK, TCR-beta, TCR-delta, TIA1, STAT3, EBER ISH

Cytogenetics

Not performed

Molecular Studies

DUSP22-IRF4 gain (74% of nuclei)

Proposed Diagnosis

Primary cutaneous anaplastic large cell lymphoma, CD30-positive, ALK-negative

Interesting Feature(s)

- The presentation for this case is unusual in that primary cutaneous ALCL typically presents as a rapidly growing erythematous ulcerated nodule or plaque and not a painful mass.
- The morphological features are also interesting in that there is usually horseshoe-shaped nuclei or donut shaped nuclei, characteristic of "hallmark" cells; this case is unique in that it looks blastoid and mimicks a myeloid sarcoma, lymphoblastic lymphoma, or high-grade B-cell lymphoma.

Panel Diagnosis: C-ALCL

A rare case of cutaneous ALK-positive anaplastic T cell lymphoma

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Case Description

Patient is a 49-year-old male with history of polysubstance use disorder and poor dentition with housing instability who presented with a rapidly enlarging mass of the submandibular neck for approximately 5 months. On physical examination, a hard indurated abscess measuring approximately 3.0 cm was palpated inferior to the right mandible without lymphadenopathy. The lesion was non-mobile, non-tender to palpation and no associated cellulitis or skin breakage was noted. CT imaging revealed a 3.6 x 4.6 x 3.5 cm heterogeneous mass, causing mass effect on the right submandibular gland but not originating from it and bilateral borderline mildly enlarged cervical chain lymph nodes. An initial biopsy was consistent with granulation tissue and necro-inflammatory debris with bacterial colonies. Interval disease progression with marked interval enlargement of the enhancing soft tissue mass overlying the right jaw, now with diffuse right masticator space invasion and enlarging bilateral cervical lymphadenopathy. An additional biopsy was diagnostic for ALK positive anaplastic T cell lymphoma.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Sections show ulcerated skin with a dermal proliferation of large, atypical cells. The cells have large, eccentric, hyperchromatic nuclei with irregular nuclear contours and prominent nucleoli. The cytoplasm is moderate and amphophilic. Mitotic figures are increased. There are abundant admixed neutrophils.

Immunophenotype

The large, atypical cells are positive for CD4, CD30, CD43, CD45, ALK, TIA-3, Granzyme B, MUM-1, c-Myc. The following T cell IHC are negative in the lesional cells: CD2, CD3, CD5, CD7, CD8. The following B cell and plasma cell IHCs are negative in the lesional cells: CD20, CD79a, CD138, IgG, OCT2, PAX5. CD10, CD56, and CD117 are negative. BCL6 is dim in scattered atypical cells, but less than 30%. BCL2 is negative. HHV8 is negative. Cyclin D1 is negative. CAM5.2, cytokeratin cocktail (AE1/AE3/PCK26), Melan-A, and SOX10 are negative in the neoplastic cells.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

ALK-positive anaplastic large cell lymphoma with immunophenotype: CD4, CD30, CD43, partial/focal CD45, ALK, TIA-3, Granzyme B, MUM-1, c-Myc

Interesting Feature(s)

This case illustrates the rapid progression of an ALK-positive cutaneous anaplastic large cell lymphoma. The cutaneous involvement of a systemic ALCL is in the differential, especially with ALK positivity, but a staging PET/CT showed a right neck mass (8.6 x 13 x 14.8 cm, SUV max 31.7) as well as small bilateral cervical hypermetabolic lymph nodes, which can be seen in cutaneous ALCL and does not influence the prognosis. The rapid progression of the lesion, as well as involvement of surrounding tissue, ruled out the diagnosis of lymphomatoid papulosis. The patient had no history or clinical evidence of mycosis fungoides.

Panel Diagnosis: Cutaneous ALK positive ALCL