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LYMPHOMA WORKSHOP SESSION 1

Primary cutaneous lymphoproliferative disorders other than mycosis fungoides / sezary syndrome

Chairs: I. Oschlies, J. Goodlad

EAHP18-LYWS-350

Primary cutaneous anaplastic large cell lymphoma with angiocentric and angiodestructive growth: an unusual and rare variant.

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Case description: 46-year-old woman with a rapidly grown ulcerated tumor on the neck.
Clinical diagnosis: Keratoacanthoma?
An excision of the lesion was performed. On radiologic staging examinations no evidence of extracutaneous disease. No relapse during follow-up period of 96 months.
Biopsy fixation details: 2 x 1.3 cm measuring skin biopsy, fixed in 4% buffered formalin
Frozen tissue available: No
Details of microscopic findings: Ulceration and dermal necrosis with hemorrhage. In the surrounding dermis and superficial parts of the subcutis dense infiltrates of cohesive sheets of medium-sized to large pleomorphic and anaplastic lymphoid cells with moderately chromatin dense, highly atypical nuclei and an eosinophilic cytoplasmic rim. Angiocentric and angiodestructive growth. Admixture of small lymphocytes and eosinophils. No significant epidermotropism.
Immunophenotype: The tumor cells express CD2, CD5, CD8 and CD30 (> 75% of the tumor cells), TIA-1, betaF1, but show no expression of CD4, loss of CD7 and are negative for CD56, TCR gamma, and ALK. EBER is negative. High proliferative activity (Ki67: 60%).
Cytogenetics: Not performed.
Molecular studies: PCR and fragment analysis showed monoclonal rearrangement of T-cell receptor gamma genes.
Proposed diagnosis: Primary cutaneous anaplastic large cell lymphoma with angiocentric and angiodestructive growth.
Interesting feature(s) of submitted case: The angiocentric and angiodestructive growth is a rare finding in primary cutaneous anaplastic large cell lymphoma (PCALCL) and represents a diagnostic pitfall as it mimicks highly aggressive primary cutaneous or secondary cutaneous T-cell non-Hodgkin lymphomas such as cutaneous gamma/delta T-cell lymphoma, peripheral T-cell lymphoma, unspecified with cytotoxic phenotype, extranodal NK/T-cell lymphoma, nasal type. Despite the growth pattern and the cytomorphology suggest a highly malignant behavior and an aggressive course, the prognosis is the excellent with a 5-year survival rate over 90% as in other histological variants of primary cutaneous anaplastic large cell lymphoma. The case should help to increase awareness for this rare and potentially diagnostically misleading variant of PCALCL.

EAHP18-LYWS-519

A Case of Lymphomatoid Papulosis with Lymph Node Involvement and Clonally Related Mycosis Fungoides

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Case description: In March 2016, a 27 year-old male patient presented with several small, in part grouped or single, waxing and waning dermal papules at the right side of the neck, the left upper arm and the left thigh. At the same time, irregular erythematous patches were noted at several sites, e.g. the abdomen. In May 2017, progression of the papules at the left thigh with focal necrosis and simultaneous enlargement of regional lymph nodes in the left groin were observed.
Biopsy fixation details: 4% neutral buffered formalin.
Frozen tissue available: No.
Details of microscopic findings: Biopsies from papules from different sites, also from the left thigh, and from different time points in 2016 and 2017 were available and illustrated diffuse and nodular deep infiltrates, sometimes accentuated around small vessels and dermal appendages. They consisted of a mixture of lymphocytes, a few granulocytes and eosinophils and medium-sized blasts that were loosely distributed, sometimes also growing in a nodular fashion, consistent with the diagnosis of lymphomatoid papulosis (LyP) type C. These biopsies showed only few intraepidermal lymphocytes and no interspersed blasts. The epidermis featured focal hyper(para-)keratosis and was otherwise unremarkable. The erythematous patchy mycosis fungoides (MF)-like areas showed a typical morphology with a partly atrophic epidermis and superficial band-like lymphoid infiltrates and also epidermotropic lymphocytes, without a mixed inflammatory background or blasts. The lymph node revealed an altered architecture giving the impression of a secondary infiltration by medium- and large-sized blasts with irregular, sometimes lobated nuclei, and focally with a perinuclear hof, coarse chromatin and several nucleoli. The background infiltrate consisted of lymphocytes and plasma cells. Extended areas showed preserved normal lymph node tissue.
Immunophenotype: The LyP blasts in the skin showed positivity for CD30, CD2, CD4, Granzyme B, Perforin and MUM1. The inflammatory background infiltrate was composed of B- (CD20+) and T-cells (CD3+, partly CD8+), with overall preserved CD7 expression. The MF cells were positive for CD3 and CD4 with expression loss of CD7 and only few small activated, CD30-positive cells. The blasts in the lymph node were positive for CD30, Granzyme B, Perforin and partly and weakly for CD2. They were negative for CD3, CD4, CD5, CD8, CD20, PAX5, ALK and LMP. The proliferation rate was high (70%).
Cytogenetics: Not done.
Molecular studies: Clonality analysis revealed the same T-Cell clone in the skin biopsies of the MF and the LyP. Clonality analysis of lymph node tissue failed because of poor DNA quality.
Proposed diagnosis: Simultaneous occurrence of clonally related MF and LyP, the latter with involvement of regional lymph nodes.
Interesting feature(s) of submitted case: Concurrent LyP and MF is a well-known phenomenon. Also, shared identical clonality of LyP and MF has been reported. However, the involvement of regional lymph nodes by large blasts poses a difficult differential diagnosis with cutaneous anaplastic large cell lymphoma (cALCL) on the one hand, and transformed MF on the other hand. A correct diagnosis is important, since conservative clinical management is recommended also in cases of LyP with regional lymph node involvement, in contrast with MF or cALCL with lymph node involvement. Recent follow-up of the case also supports the diagnosis of LyP, since regression not only of the skin lesions, but also of the lymph node enlargements in the left groin have been recorded without therapy.

EAHP18-LYWS-277

A case of a Recurrent Primary Cutaneous CD30+ Lymphoproliferative Disorder with DUSP22 rearrangement.

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Case description: A 62 year old male presented for the first time in 2011 with an isolated tumor of the left thigh diagnosed as a primary cutaneous CD30+ anaplastic large T cell lymphoma (PC-ALCL). He did not have previous medical history. He completed remission after surgery and radiation therapy but the disease recurred one year later (left forearm, gluteal fold). A CT scan in January 2013 was negative and he received Methotrexate until complete remission. From September 2014 to 2016 two lesions appeared (right foot, right arm) that were surgically removed. He lastly presented with a flare of papules on the lower limbs.
Biopsy fixation details: Formalin-fixed paraffin-embedded tissue
Frozen tissue available: No
Details of microscopic findings: The five specimens removed showed similar biphasic histopathological features with a dense intradermal lymphoid infiltrate composed of moderately to large cells with occasional “hallmark” cells associated with a striking epidermotropism of smaller atypical lymphocytes, featuring a reticuloid pagetoid-like pattern. Pilotropism was also present.
Immunophenotype: Tumoral T lymphocytes showed a strong CD3 positivity. CD4, CD8, CD2, CD5, CD7, TCRBeta, ALK, EBV, cytotoxic markers were negative. CD30 showed a membranous strong positivity on dermal lymphocytes and a slightly dimmer stain on epidermotropic cells. A reactive lymphocytic infiltrate was associated, composed of small T and B lymphocytes.
Cytogenetics: A break-apart FISH technique showed a rearrangement of the DUSP22-IRF4 locus on the 6p25.3 gene
Molecular studies: Monoclonal rearrangement of the TCRG gene
Proposed diagnosis: Primary Cutaneous Lymphoproliferative Disorder with DUSP22 rearrangement
Interesting feature(s) of submitted case: Our patient presented with a recurrent PC-ALCL without systemic involvement. The five lesions collected throughout time showed similar biphasic histopathological features that harbored a rearrangement of DUSP22on the locus of the 6p25 gene. In 2009, an article described for the first time a subset of PC-ALCL featuring this rearrangement(1). Two others followed but corresponding cutaneous lesions did not show epidermotropism(2,3). The first report of these features (2013) interested a series of lymphomatoid papulosis with chromosomal rearrangement of 6p25(4). These specific histological features were suspected to be related to this translocation(5,6). DUSP22 rearranged PC-ALCL could be associated with regional lymph node spread or cutaneous relapse(7). Differential diagnosis include a secondary localisation to the skin of a systemic ALCL and, less likely, a CD30+ transformed mycosis fungoides. This rearrangement has been recently encountered in systemic ALK-negative ALCL. This entity was considered as provisional and recent works showed that a subset of these tumors harbored a rearrangement of the 6p25.3 gene, associated with a prognosis comparable to ALK-positive ALCLs'(8,9). However, most of these tumors did not extend to the skin. Only one article described a secondary cutaneous localisation of a DUSP22 rearranged s-ALCL. Both primary and cutaneous lesions shared same phenotypic and genotypic features and the specific histopathological cutaneous biphasic pattern was also present(10).

(1)Pham-Ledard et al.J Inv Dermatol.2010;130,816–825.
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(7)J Inv Dermatol.2013;133,1680–1682.
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(10)Histopathology.2015;67(6):932–935.

EAHP18-LYWS-142

Atypical CD4+ lymphocytic proliferation in the skin: T-cell pseudolymphoma, cutaneous CD4+ small/medium-sized lymphoproliferative disorder or cutaneous peripheral T-cell lymphoma, NOS

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Case description: 61-year-old female with a 25-year history of recurrent bilateral invasive breast carcinoma NST under therapy (anastozole, denosumab) presenting with progressive multiple pruritic erythematous oval papules on left shoulder and forearms for 6 months. No evidence of extracutaneous tumor identified in PET-CT. A surgical biopsy was performed of the solitary papule on the left shoulder.
Biopsy fixation details: Skin biopsy, 2 cm x 1,3 cm x 0,4 cm, fixed in 4% buffered formalin.
Frozen tissue available: No
Details of microscopic findings: The entire dermis showed nodular confluent infiltrates of predominantly small lymphocytes with round nucleus with dense chromatin, small lymphocytes with irregular nuclear borders and lymphocytes wtih medium-sized nucleus, less dense chromatin and showing a small cytoplasmic rim. Intermingled some large blasts in the lower dermis. Randomly admixed histiocytes forming some epitheloid granulomas and few plasma cells. No epidermotropism, no eosinophils, no lymphoid follicles with germinal centers.
Immunophenotype: The lymphocytes were predominantly CD4+ with a high number of CD8+ cells, some expressing TIA-1 without loss of T-cell antigens. 10% of the lymphoid T-cells, usually the medium-sized cells expressed PD-1 and partially bcl6. No expression of CD10, CD15, CD56, ALK1 or EMA. The intermingled blasts were CD4+ CD30+(<5% of the infiltrate). Focally aggregates of CD20+ B-lymphocytes (20% of the infiltrate). The Ki-67 proliferation index of the lymphoid cells was 10-20%. EBER in-situ-hybridization was negative.
Cytogenetics: Not performed.
Molecular studies: PCR (BIOMED) and fragment analysis showed no monoclonal rearrangment of the T-cell receptor gamma chain gene.
Proposed diagnosis: T-cell pseudolymphoma in the skin, consistent with a manifestation of a lymphomatoid drug reaction.
Interesting feature(s) of submitted case: The histology of the skin papule showing nodular infiltrates with predominance of small T-lymphocytes and admixture of medium-sized T-lymphocytes is compatible with nodular T-cell pseudolymphoma, but fullfills also the histologic and immunophenotypic criteria of cutaneous CD4+ small/medium-sized T-cell lymphproliferative disorder. For the latter entity a multifocal occurence is very unusual and has been associated with an aggressive course. Unusual features for a PTCL, NOS, as an additional differential diagnosis, are the clinical presentation, the predominant small/medium-sized morphology of the infiltrating T-cells as well as the low number of CD30+ T-blasts. Within 8 months partial resolution wth recurrence of itching and some tiny papules on forearms and arms was observed. A punch biopsy (histology not shown) revealed discrete perivascular T-lymphocytic infitrates without atypia, few admixed B-cells and isolated middle-sized CD30+ T-blasts in the mid dermis, again without detectable T-cell clonality.
The course of the disease with regression of the papular leions allowed the exclusion of a T-cell lymphoma and permitted a definitive diagnosis of a T-cell pseudolymphoma, consistent with a manifestation of a lymphomatoid drug reaction (either to anastozole or to denosumab). The case highlights the challenges in the classification and terminology of dermal atypical CD4+ small to medium-sized lymphocytic infiltrates with multifocal presentation and illustrates the importance of clinicopathologic correlation including follow-up (Mitteldorf C, Kempf W; 2017. Cutaneous Pseudolymphoma. Surgical Pathology 10: 455-476)

EAHP18-LYWS-179

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

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Case description: An 87-year-old male patient presented with a 5.5 cm firm, nodular tumor on the right medial thigh and a 3.6 cm semicircular erythematous plaque on the right knee. Both lesions had been present for approximately one month and were asymptomatic. Biopsies were obtained. A PET-CT scan revealed increased uptake at the site of the right medial thigh nodule, but no extracutaneous disease. The patient was treated with localized radiation therapy to the right medial thigh with complete resolution.
The patient was subsequently asymptomatic for 13 months until developing a 4 cm erythematous plaque on his medial left elbow. Biopsy demonstrated recurrent disease. The patient received localized radiation therapy with complete resolution of the lesion. 32 months following diagnosis, the patient developed multiple disseminated cutaneous plaques (>50) over a large area of his trunk. He was treated systemically with vorinostat, and died 41 months following the initial diagnosis.
Biopsy fixation details: Neutral-buffered formalin
Frozen tissue available: No
Details of microscopic findings: The initial biopsy (right medial thigh) reveals a dense atypical lymphoid infiltrate in the superficial and deep dermis. Mild epidermotropism is present. The atypical cells are medium to large, display round to irregular nuclear contours, open chromatin, and occasionally prominent eosinophilic nucleoli. Mitotic figures and apoptotic bodies are frequent. No necrosis, epidermal ulceration, or periadnexal invasion is present. The concurrent right knee biopsy demonstrates similar morphologic features.
Biopsy of the recurrent lesion (medial left elbow) demonstrates focal and variably-sized aggregates of atypical lymphoid cells that are occasionally epidermotropic, periadnexal, and perivascular. The neoplastic cells are morphologically similar to those seen in the original specimen with more prominent epidermotropism and periadnexal invasion.
Immunophenotype: Immunohistochemistry performed on the initial lesion demonstrates the neoplastic cells to be positive for CD2, CD3, CD8, CD43, CD45, BCL2, perforin, TCR-beta, and have a Ki-67 proliferation index of approximately 80%. The neoplastic cells are negative for CD1a, CD4, CD5, CD7, CD30, CD34, CD45RO, CD56, CD57, CD79a, CD117, Granzyme B, Pax5, and LMP1. TIA-1 staining is non-contributory due to a high background. In-situ hybridization is negative for EBER1.
The immunophenotype of the recurrent lesion is identical to the original except for CD45RO positivity. Increased CD3+ CD4+ T cells with small, condensed nuclei are more prominent in the recurrent lesion.
Cytogenetics: Not performed
Molecular studies: A monoclonal T cell receptor gamma chain gene rearrangement was demonstrated in the right medial thigh lesion (initial diagnosis), and an identically-sized rearrangement was present in the recurrence.
Proposed diagnosis: Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma
Interesting feature(s) of submitted case: 1) The immunophenotype of the lesional cells is consistent with PCAECTL, although the absence of granzyme B staining is unexpected in a lesion with a cytotoxic T cell phenotype.
2) The recurrent lesion recapitulates many of the key features of the original case with more prominent epidermotropism and periadnexal invasion, typical findings in PCAECTL. The acquisition of CD45RO expression at relapse is of uncertain significance and is unusual for PCAECTL. Increased numbers of CD3+ CD4+ T cells are noted in the recurrent lesion and one might speculate that they may represent an anti-tumor response, one possible contributor to the relatively indolent clinical course.

EAHP18-LYWS-563

Indolent Epidermotropic Gamma Delta T-cell Lymphoma

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Case description: The patient is a 40-year-old Caucasian male, who initially presented in 2008 at an outside institution with small papules with partial crusting and central ulceration. A diagnosis of pityriasis lichenoides /PLEVA was made due to histopathologic findings; however, from subsequent biopsies in 2009, a diagnosis of mycosis fungoides, tumor stage was made. Due to recurrence after chemotherapy, the patient underwent allogenic stem cell transplant in 2011. In 2013, he noticed cutaneous lesions and biopsy showed recurrent disease and was treated with chemotherapy.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: Sections show acanthotic and irregular epidermis with alternating parakeratosis and orthokeratosis. Numerous dyskeratotic and apoptotic keratinocytes are noted throughout the epidermis. Exocytosis and tagging of numerous atypical lymphocytes at the dermoepidermal junction associated with vacuolar basaloid degeneration is noted. The atypical lymphocytes show large nuclei with fine chromatin and prominent nucleoli, some with haloes. Spongiosis is noted. The superficial dermis shows a perivascular and interstitial lymphohistiocytic infiltrate with rare plasma cells.
Immunophenotype: The atypical lymphocytes are negative for CD4 and CD8, positive for gamma-delta T cell receptor, CD3 and CD7 with partial loss of CD5 expression. CD56 is negative; partial expression of TIA-1 and granzyme B is noted. BF1 (alpha/beta TCR) is negative. Numerous large cells are positive for CD30 (15%). In situ hybridization for EBV is negative.
Cytogenetics: NA
Molecular studies: Positive for T-cell receptor gene rearrangement
Proposed diagnosis: Primary cutaneous epidermotropic indolent gamma delta T-cell lymphoma
Interesting feature(s) of submitted case: The morphologic findings are reminiscent of mycosis fungoides, but characterized by a cytotoxic epidermal infiltrate of atypical lymphocytes causing vacuolar degeneration of the basaloid layer, dyskeratotic and apoptotic keratinocytes, and ulceration. The atypical lymphocytes are negative for CD4 and CD8, expressing a gamma-delta T cell phenotype, positive for CD3 and CD7 with partial loss of CD5 expression. CD56 is negative; partial expression of TIA-1 and granzyme B is noted. BF1 (alpha/beta TCR) is negative. Numerous large cells are positive for CD30 (15%). Overall, the findings are consistent with a gamma delta T cell lymphoma with epidermotropic features and an indolent clinical course.

EAHP18-LYWS-355

Primary Cutaneous Acral CD8 positive T cell lymphoma involving the lower leg

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Case description: A 32-year-old male presented with a red lump on his right leg that he noticed about 4 years ago. He has a past medical history of osteomyelitis involving the left leg which was treated with antibiotics and surgical intervention. PET/CT scan was performed that demonstrated low-level hypermetabolic activity at the proximal, medial subcutaneous tissue in the right lower extremity with SUV of 1.5. An incisional biopsy was performed in March 2016. The case was submitted to MSKCC for consultation
Biopsy fixation details: Tissue specimens were fixed in 10% formalin
Frozen tissue available: NA
Details of microscopic findings: Histologic sections of skin biopsy show a diffuse dermal atypical lymphoid infiltrate extending into subcutaneous tissue. The atypical lymphoid cells are monotonous, medium-sized with irregular/ frequently folded nuclei, small nucleoli, fine chromatin, and a moderate amount of pale cytoplasm. There was no epidermotropism present. Perivascular and periadnexal involvement is noted. Angiodestruction and necrosis are not present
Immunophenotype: The neoplastic lymphoid cells strongly express CD3, CD2, CD5, CD8, TIA1, BCL2, BCL6, while are negative for CD20, CD7, CD4, CD30, ALK1, granzyme B, CD25, CD10, CD56, MUM1, CD43. The proliferation fraction was approximately 15%. EBER in situ hybridization was negative. CD21 highlight rare follicular dendritic cell meshwork
Cytogenetics: NA
Molecular studies: PCR studies demonstrated clonal TCR gamma gene rearrangement.
Comprehensive genomic profiling studies (MSK IMPACT) were performed at MSKCC that showed following mutations;1. PTEN (NM_000314 - 10q23.31) Deletion (Fold Change: -2.5) and 2. BMPR1A (NM_004329) Rearrangement: c.1342+83:BMPR1A_chr10:92944869del
Proposed diagnosis: Primary Cutaneous Acral CD8 positive T cell lymphoma involving the lower leg
Interesting feature(s) of submitted case: Primary Cutaneous Acral CD8 positive T cell lymphoma is a recently recognized indolent CD8 positive lymphoproliferative disorder. The entity is rare among cutaneous T-cell lymphomas and typically presents with solitary skin lesions at acral sites. The majority of lesions are located on the ears and nose, bilateral and multiple symmetrical presentations have been described. The discrepancy between the indolent presentation and behavior of these lesions with the histologically aggressive features often poses problems in diagnosis and these cases are commonly misclassified as peripheral T-cell lymphoma, NOS, which indicates an aggressive clinical course. Differentiation from otherwise aggressive T-cell lymphomas bearing a cytotoxic CD8+ phenotype, in particular from primary cutaneous aggressive epidermotropic CD8 + T-cell lymphoma is fundamental to avoid unnecessary harmful treatment. This case is a typical example of Primary Cutaneous Acral CD8 positive T cell lymphoma but shows unique lower leg involvement, which has not been documented. To our knowledge, no other case of primary cutaneous CD8 positive T cell lymphoma involving the lower leg has been reported in the literature. In addition to classical morphological and immunophenotypic features, our case showed clonal TRG gene rearrangement and deletion involving PTEN gene. This tumor is known to have an indolent course and favorable prognosis. Complete remission after surgical excision or radiotherapy is the rule. Recognition of this entity with an indolent clinical behavior is important to avoid overtreatment. The patient was treated with the total dose of 3000 cGy over tumor bed of right lower extremity. The treatment was completed in June 2016. Follow up examination showed no clinical or radiological evidence of disease.

EAHP18-LYWS-232

Primary cutaneous follicle center lymphoma (WHO 2016) composed of predominantly large cells.

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Case description: A 75-year-old male presented in 10/2017 with a 3.5 cm scalp mass. He had no prior hematologic malignancy. PET CT scan revealed the FDG avid nodule in the left scalp and an FDG avid nodule in the right parotid gland that was biopsied later to be Warthin's tumor.
Biopsy fixation details: Formalin.
Frozen tissue available: No.
Details of microscopic findings: Sections show a portion of skin involved by an atypical lymphoid infiltrate within the dermis growing in a predominantly diffuse pattern without discrete follicles. It shows a prominent Grenz zone. The neoplastic cells are medium to large in size with irregular nuclei, fine chromatin, occasional prominent nucleoli and a spindled appearance in some areas.
Immunophenotype: Positive for: CD20, PAX5, BCL6, and BCL2(dim) and negative for CD3, CD5, CD10, CD43, MUM1, FOXP1, EBV-ISH. Ki-67 proliferation index of 50%. No significant CD21 or CD23-positive follicular dendritic meshworks.
Cytogenetics: FISH for t(14;18) negative.
Molecular studies: Clonal IgH and IgK gene rearrangement.
Proposed diagnosis: Primary cutaneous follicle center lymphoma (WHO 2016) composed of predominantly large cells.
Interesting feature(s) of submitted case: This is an interesting case of primary cutaneous B-cell lymphoma with the morphology of a large cell lymphoma, but without the characteristic morphologic or phenotypic features of a primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT). Cases such as these can be somewhat difficult to classify within the 2016 WHO-defined cutaneous B cell lymphomas. The only primary cutaneous DLBCL specifically noted by the WHO is PCDLBCL-LT, which characteristically has immunoblastic morphology and a non-germinal center B cell (non-GCB) phenotype. Thus, the best, albeit imperfect, fit for cases such as these is primary cutaneous follicle center B-cell lymphoma (PCFCL). PCFCL is described by the WHO as being composed of predominantly centrocytes with variable number of centroblasts, although cases with predominantly centroblasts do occur. These cases are challenging, as it is often not known to the pathologist whether this represents a systemic disease with cutaneous involvement (DLBCL, NOS) or primary cutaneous disease (PCFCL).
The existence of PCDLBCL-NOS has been evaluated in the recent study by Lucioni et al., which identified 40 cases that did not belong to either PCFCL or PCDLBCL-LT based on cytology and/or architecture.[1] In this cohort, PCDLBCL-NOS had a clinical presentation more similar to PCFCL while demonstrating morphologic features more consistent with a DLBCL. Clinical behavior was quite similar to the PCFCL group, especially in DLBCL with a GCB phenotype, suggesting that these may simply represent a spectrum of PCFCL cases composed of predominantly large cells.
Another study by Plaza et al. acknowledges the presence of cutaneous lymphoma cases in which there are residual germinal centers within a diffuse neoplastic population of large B cells. They suggest that this may indicate the transformation of preexisting cutaneous low-grade B-cell lymphoma to PCDLBCL, though the presence of a characteristic immunohistochemical profile may favor these simply to represent PCFCL with varying morphology.[2]
Overall, this case illustrates a challenge to hematopathologists to confidently define cutaneous follicle center B cell lymphomas. An accurate diagnosis in this setting is of paramount importance for clinicians to provide best therapy and accurate prognostic information.

EAHP18-LYWS-103

Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement

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Case description: A 69-year-old woman presented with a single erythematous and nodular lesion on her left cheek, rapidly growing by more than 2 cm in two weeks. No peripheral adenopaties were present, and additional laboratory and imaging studies showed no abnormalities The lesion was surgically excised and there was no evidence of disease in the 7 months of follow-up.
Biopsy fixation details: Five-mm-thick tissue slices were fixed in 10% neutral-buffered formalin, then removed from formalin, processed, and paraffin-embedded. Four-µm paraffin sections were stained with haematoxylin and eosin.
Frozen tissue available: No frozen tissue was available.
Details of microscopic findings: Histological examination showed a nodular and diffuse infiltration of the deep and superficial dermis by large- and medium-sized pleomorphic cells. The overlying epidermis exhibited a pagetoid reticulosis-like intra-epidermal lymphocytosis by small-to-medium sized cells with cerebriform nuclei and irregular contours. The dermal lymphocytes were larger, with marked pleomorphism, pale nuclei and vesicular chromatin, and several nucleoli. Large cells were intermingled with hallmark cells, and mitotic figures were abundant.
Immunophenotype: Neoplastic cells were positive for CD30, CD3, and TCR-βF1, and negative for CD20, CD4, CD8, TCR-γ and ALK.
Cytogenetics: FISH analyses were performed on 3-µm tissue sections using an IRF4-DUSP22 (6p25.3) break-apart probe (KBI-10613; Kreatech, Leica, Spain) producing a split signal that indicated a 6p25.3 rearrangement.
Molecular studies: No molecular studies were performed.
Proposed diagnosis: Primary cutaneous anaplastic large cell lymphoma with 6p25.3 rearrangement.
Interesting feature(s) of submitted case: CD30-positive primary cutaneous lymphoproliferative disorders include several entities with differing clinical presentation but overlapping histological features, including lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (cALCL). Furthermore, they must be differentiated from cutaneous involvement by systemic ALK-negative anaplastic large cell lymphoma (sALCL).
The study of 6p25.3 rearrangement was initially described as a useful tool in the differential diagnosis of cALCL and sALCL with secondary cutaneous involvement, being indicative of the former (20–57% of cALCLs)[1]. However, DUSP22–IRF4 locus translocation was later on also described in LyP, in association with a particular biphasic histological pattern [2], and in sALCL[3]. Herein, we report the case of cALCL in a patient with a solitary, nodular and rapidly growing lesion on the cheek, showing the same striking biphasic histological pattern previously described in LyP. This data suggests this histological pattern could be indicative of a primary cutaneous neoplasm, being useful in the differential diagnosis between cALCL and secondary skin involvement by sALCL[4].

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EAHP18-LYWS-107

Cutaneous acral CD8+ T-cell lymphoma

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Case description: 69-year-old man with recurrent, painful swelling and redness of both ears for the last two years. Staging investigations negative.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: Dense, diffuse lymphoid infiltration within the dermis without involvement of the epidermis and with a grenze zone. Medium-sized pleomorphic lymphocytes predominate. No significant number of eosinophils, neutrophils, or plasma cells.
Immunophenotype: CD3+, CD5+, CD4-, CD8+, CD30-, TIA-1+ Granzyme B+, CD56-. Proliferation rate (MIB-1/Ki67) 10%.
Cytogenetics: Not done.
Molecular studies: PCR of TCR genes: polyclonal smear; PCR for Borrelia burgdorferi DNA: negative.
Proposed diagnosis: Primary cutaneous acral CD8+ T-cell lymphoma
Interesting feature(s) of submitted case: Typical presentation of a rare entity of extranodal (cutaneous) T-cell lymphoma

EAHP18-LYWS-112

Primary cutaneous anaplastic large cell lymphoma with aberrant histology & immunophenotype

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Case description: 42 years old male with a excisions biopsy (Sep. 2017) for a subcutaneous tumour process (26 mm in largest diameter) along with 2 small tumour satellites (7mm, 7mm) in the right breast region. Rapid tumour growth within the past few weeks. Clinical diagnosis is obs. malignant melanoma. History of curettage a month before the excision. Debut was in 2015 & clinically assessed as an epithelial inclusions cyst, no biopsy.
Biopsy fixation details: routinely formalin fixed in 10% neutral buffered formalin for 48 hours & paraffin embedded.
Frozen tissue available: no, as the tissue is recieved with the diagnosis obs. Melanoma, so material for Flow & lymphoma biobank has not been taken
Details of microscopic findings: tumour process consisting of large lymphocytes involving dermis & extending to the subcutis and the deep resection margins. There is central ulceration, polypous process with nodular side margins. No epidermotropism. Lymphocytes are large but not typically anaplastic, have more of a centroblast morphology with many mitosis. The satellite tumours also have the same morphology.
Immunophenotype: CD45 negative with universal & strong CD30 positive cells. 90% of the cells are Ki67 positive. ALK & EMA negative. CD3, CD8, CD5, CD7, TIA, Granzym & EBER (EBV-ISH) all negative. CD2 positive, CD4 negative. BCL2 & MUM1 positive. CD15 positive with stippled reaction.
All B cell markers negative (CD20, CD79a, PAX5, BCL6, CyD1 & surface immunoglobulins). Other negative markers: CK8/18 CK7, CK20, S100, SOX10, Synaptophysin, CD56, CD68, CD117, CD138, CD38
Cytogenetics: none
Molecular studies: FISH **t** (2; 5) negative
Proposed diagnosis: Primary cutaneous Anaplastic Large Cell Lymphoma
Interesting feature(s) of submitted case: Diagnosis of exclusion as the histomorphology is not typically anaplastic, no big prominent nucleoli's & no typical Hallmark cells. There is a T- phenotype with a CD2 positive lymphocytes but all the other T markers including the markers for cytotoxic proteins are negative.
Points in favour of ruling out a PTCL-NOS are lack of CD45 & other T-cell markers except CD2.
All B-cell markers are also negative so a Large B-cell lymphoma is also ruled out.
Lymphoma does not have a Hodgkin's histomorphology.
Follow up - No bone marrow or disseminated disease on PET scans. Bone marrow biopsy with normal marrow findings.

EAHP18-LYWS-118

Primary cutaneous marginal zone lymphoma with plasmacytic differenciation and amyloid in setting of several autoimmune diseases.

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Case description: 62 year old female presented in July 2014 with nodular skin lesion at left hemithorax measuring 1 cm in diameter. Anamnesis revealed multiple autoimmune disorders including Sjögren syndrome (since 2008), multiple sclerosis (since 2010), autoimmune hepatitis (since 1994), asthma (since 1994) and thyreoiditis with hypothyreosis (since 2004).
Lesion was excised and sent for second opinion to our Department.
Biopsy fixation details: Buffered formalin.
Frozen tissue available: Not available.
Details of microscopic findings: Skin excision showed atrophic epidermis and dermis infiltrated with amorphous eosinophilic material consistent with amyloid (Kongo red/Saturn red positive) with focal granulomatous reaction.
In periadnexal and perivascular areas there quite subtle infiltitrates predominantly consisting of plasma cells and fewer lymphocytes. Sheets of large cells, necrosis or increased mitotic activity was not found.
Immunophenotype: Kongo red, Saturn red – positive in amorphous material, positive yellow-green birefringence in polarized light. Perivascular infiltratates composed of minority of B-cells (CD20) and majority of plasma cells (CD138) with clear restriction of lambda chain expression (kappa in few cells). Admixed CD3+ T-cells.
Immunoflurescence:
Direct immunofluorescence revealed positivity of lambda chain in plasma cells and amyloid deposits. Kappa stained in few plasma cells, deposits were negative.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Primary cutaneous marginal zone lymphoma (PCMZL) with extensive plasmacytic differentiation and amyloid production.
Interesting feature(s) of submitted case: Evolution of marginal zone lymphoma in the setting of autoimmune disease is a known risk. Presented case is showing very subtle cutaneous involvement with low-grade B-cell lymphoma with plasmacytic differentiation and with extensive amyloid production (amyloidoma) in a patient with multiple autoimmune disorders. Staging confirmed pobably localized infiltration of skin, infiltration of salivary glands. lymph nodes or bone marrow was not proved. Patient is in watch and wait surveillance without signs of progression (3/2017).

EAHP18-LYWS-130

Primary Cutaneous Follicle Center Lymphoma with mutational analysis.

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Case description: A 55-year-old female with no significant past medical history presented with a red indurated 2.0 cm nodule on the left side of neck believed to be an irritated/ruptured, non-draining epidermal inclusion cyst, pseudofolliculitis or some other cyst. Following her skin excision, staging bone marrow examination and PET-CT scans were negative. The patient has been disease free for six years to date.
Biopsy fixation details: Formalin-fixed paraffin-embedded tissue.
Frozen tissue available: NA.
Details of microscopic findings: The histologic sections demonstrate skin with a grenz zone and a dense follicular-appearing dermal lymphoid infiltrate that dissects collagen bundles and extends into the subcutaneous tissue. Some of the follicular structures are well defined and surrounded by small lymphocytes and others very ill-defined and irregular. They are composed of numerous variably sized but often intermediate to large centrocytes with some centroblasts and occasional cells consistent with follicular dendritic cells.
Immunophenotype: CD20 highlights numerous positive cells within the follicles that are CD10, BCL6, HGAL and MEF2B positive. They are BCL2, CD5, CD43, IRF4/MUM1 and cyclin D1 negative. Cells with a similar germinal center phenotype were also present outside of the well-defined follicles infiltrating the collagen bundles. CD3 stains numerous small lymphoid cells in the interfollicular regions. CD21 demonstrates expanded, distorted follicular dendritic cell meshworks. Ki-67 highlights a moderate number of cells in the follicular areas. Kappa and lambda stains did not demonstrate plasmacytic differentiation but were otherwise difficult to interpret because of background staining.
Cytogenetics: FISH study using a BCL2 break-apart probe was negative.
Molecular studies: Next generation sequencing using a targeted hybrid-capture on genomic DNA extracted from formalin-fixed paraffin-embedded tissue was performed. A custom probe panel comprising 4099 targets in the coding regions of 220 genes known to be recurrently mutated in B cell lymphoma was used. Non-synonymous variants (NSVs) and insertions/deletions were recorded except those that may represent germline variants with allele frequencies between 40-60%. Mutations were identified in TNFRSF14 (p.C138Y) with an allele frequency of 24%, FOXO1 (p.T24I) with an allele frequency of 11% and SOCS1 (p.R172Pfs*74) with an allele frequency of 11%.
Proposed diagnosis: Primary Cutaneous Follicle Center Lymphoma (PCFCL).
Interesting feature(s) of submitted case: This typical PCFCL is a part of a series of similar cases that demonstrate a molecular landscape that appears to be distinct from nodal follicular lymphomas, further justifying their classification as a distinct entity. Molecular studies demonstrated TNFRSF14, SOCS1 and FOXO1 mutations. These mutations are reported in approximately 17-41%, 2-17% and 4-27% of FL, respectively. There was no evidence of a KMT2D mutation which is a part of the molecular landscape of many conventional follicular lymphomas (reported to be present in approximately 73% of FL -- 36-82% in individual studies). In spite of their distinct nature, this case also further supports the germinal center origin of PCFCL with expression of MEF2B and HGAL, two additional germinal center markers which we found to be positive in all the PCFCL we studied.

EAHP18-LYWS-133

pcALCL presenting as a single nodule on the right knee.

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Case description: A 36 year-old female presents with a single nodule of the right knee, (1.5 cm. in maximum dimensions). Clinically, thought to be a dermatofibroma. Thorough physical, including a skin exam, showed no other lesions.
Biopsy fixation details: 4.0 mm punch biopsy placed in neutral buffered formalin.
Frozen tissue available: NA
Details of microscopic findings: Sections demonstrate an ulcerated epidermis with an underlying nodular and interstitial infiltrate by large and small lymphoid cells. The large cells showed a spherical nucleus with an identifiable nucleolus. A moderate number of mitotic figures were seen. A mild infiltrate by inflammatory cells was also noted.
Immunophenotype: Immunohistochemistry demonstrated that the infiltrate was a T-cell proliferation reacting with CD2, CD3, CD5, and CD4. BetaF1, CD7, and CD8, stained only with reactive lymphocytes. Additional stains showed that the infiltrate was CD30 positive, ALK-1 negative, MUM-1 positive, and TIA-1 negative. EMA, CD56, CD20, and CD10 were negative. BCL2 identified the T-cell lymphoproliferative process.
Cytogenetics: NA
Molecular studies: T-cell gene rearrangement demonstrated both Beta and Gamma clonal reaarrangement.
Proposed diagnosis: CD30 lymphoproliferative disease; probable primary cutaneous anaplastic large cell lymphoma.
Interesting feature(s) of submitted case: This case demonstrated that BetaF1 and TIA-1 were negative; suggesting the probable diagnosis of primary cutaneous anaplastic large cell lymphoma.

EAHP18-LYWS-141

Primary cutaneous anaplastic large cell lymphoma with subsequent aggressive widespread dissemination

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Case description: A 73-year-old woman presented with a 3-4 week-old left upper arm lesion. It started as 3 "bumps" ; one resolved while one enlarged after antibiotics. On exam (07/09) there was a 7x8 cm indurated area with a bloody protruding 2x2 cm area and a 1 cm indurated area below the larger lesion (#1). PET/CT and peripheral blood flow cytometry (08/09) were negative for disseminated disease. Within a month eight new lesions appeared on the same arm (not biopsied). After radiation therapy (09/09) there was marked improvement (reduced 75%) and no new lesions or lymphadenopathy. In 11/09 she developed a hip fracture and arthroplasty was performed (#3). A 4x3 cm periumbilical eschar present was also biopsied (#2). A pleural effusion developed (01/10, #4). She expired a few days later, 6 months after onset of skin lesions.
Biopsy fixation details: Specimens were fixed in 10% formalin. The bone was also acid-decalcified.
Frozen tissue available: None
Details of microscopic findings:
#1. Skin, left arm (submitted, 07/09): The skin showed a vaguely nodular subcutaneous/dermal inflammatory infiltrate with pseudoepitheliomatous hyperplasia. The cells were predominantly neutrophils with some peripheral lymphocytes. Large markedly atypical cells were present scattered throughout or in small groups. These had vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm.
#2. Skin, abdomen (12/09): There was a dense dermal infiltrate of large atypical cells with markedly pleomorphic nuclei mixed with neutrophils. The large cells were more abundant than in the arm lesion.
#3. Bone, right femoral head (12/09): The marrow space was replaced by large atypical cells with markedly pleomorphic nuclei and moderate amounts of eosinophilic cytoplasm.
#4. Pleural fluid, left (01/10): Large atypical cells with markedly pleomorphic nuclei were present.
Immunophenotype:
#1.Positive: CD30 (strong, Golgi), CD4, CD5, CD2 (dim), perforin
Subset: CD3, CD43, TIA1, EMA, CD45RO, granzyme B, P63 (dim)
Negative: CD8, CD20, CD45, CD56, CD79a, ALK, S100, HMB45
#2.Positive: CD30
Negative: ALK
#3.Positive: CD30, CD5, MUM1
Subset: EMA, CD45RO
Negative: CD3, CD4, CD8, CD20, CD45, CD138, AE1/AE3, CAM5.2, CK903, S100
#4.Positive: CD30, CD45
Negative: AE1/AE3, CD3
Cytogenetics: N/A

Molecular studies: PCR for TRG rearrangements was attempted on #1 and #3. #1 showed clonal rearrangement, however DNA from decalcified #3 did not amplify.
Proposed diagnosis: Primary cutaneous anaplastic large cell lymphoma with subsequent aggressive widespread dissemination
Interesting feature(s) of submitted case: This CD30+ lymphoproliferative disorder was initially restricted to the skin and briefly improved before rapidly disseminating and killing the patient. It could represent either a primary cutaneous anaplastic large cell lymphoma (PC-ALCL) which progressed to systemic involvement, or a systemic ALK-negative ALCL initially only apparent in the skin. Rearrangements of TP63 have been linked to a worse prognosis in both entities and are usually accompanied by overexpression of the protein.
Arguing for this to be a primary cutaneous process, at presentation the lesions were localized to the skin with no evidence of disseminated disease. In addition, the lesion initially responded well to local radiotherapy, with significant clinical improvement. PC-ALCL typically has an indolent course with 85% 5-year survival, but patients with "extensive limb disease" at presentation have a more aggressive course and distinctly different gene expression profile than typical indolent PC-ALCL cases. This case seems to typify this (perhaps not well recognized) subtype.

EAHP18-LYWS-155

52 year old male presenting with cheek patch diagnosed as pseudolymphoma for 3 years. Flow cytometry aids in diagnosis of primary cutaneous marginal zone lymphoma at year 4.

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Case description: 52 year old male with red hued patch on cheek. First noticed as a small red bump in 2013/14. Biopsy in 2014 diagnosed as pseudolymphoma, treated with topical steroids for two weeks without resolution. Lesion continued to grow, with biopsies in 2015 and 2016 diagnosed as pseudolymphoma. Biopsied again in 2017 with fresh tissue submitted for flow cytometry.
Biopsy fixation details: 10% Neutral Buffered Formalin
Frozen tissue available: n/a
Details of microscopic findings: H&E stained sections show a skin punch biopsy with a variably dense, somewhat nodular dermal lymphoid and plasmacytic infiltrate. The lymphocytes are small to intermediate in size with associated plasma cells (some areas more numerous than others). Immunohistochemical stains show the lymphoid infiltrate consists of mixed CD20 positive B cells and CD3 positive T cells with no aberrant expression of CD10, CD43, Cyclin D1 or BCL6. In situ hybridization for kappa and lambda light chain expression reveals the plasma cells are lambda light chain restricted
Immunophenotype: Positive: CD11c, CD19, CD20, lambda light chain
Negative: CD3, CD5, CD10, CD43, BCL6, Cyclin D1
Cytogenetics: n/a
Molecular studies: PCR: Clonal B cell / immunoglobulin gene rearrangement
Proposed diagnosis: Primary cutaneous marginal zone lymphoma
Interesting feature(s) of submitted case: Prominent reactive T cells and B cells are present, hiding the smaller clonal B cell population. The patient had 3 prior biopsies (2014, 2015, 2016) diagnosed as pseudolymphoma. Immunostains were not performed at the 2014 time point. Immunostains on the 2015 biopsy showed was a mix of B cells and T cells with polytypic plasma cells. The immunostains at the 2016 time point showed more prominent B cell aggregates than before, but plasma cells were still polytypic (although slight lambda skew was noted at that time). 2017 time point was still a challenging diagnosis, with numerous admixed polyclonal B cells and T cells, with the lambda monoclonal B cells accounting for 1% of the white cells by flow cytometry. Could invoke a “monoclonal B lymphocytosis” type diagnosis; however, the clinical course would support the diagnosis of lymphoma. Patient received electron beam radiation to the area with resolution.

EAHP18-LYWS-172

Subcutaneous Panniculitis-like T-cell Lymphoma

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Case description: A woman in her 60s presented with a three-year history of recurrent fevers, night sweats, fatigue, myalgias, arthalgias and widespread painful subcutaneous nodules necessitating multiple hospital admissions. On examination, she was ill-appearing and febrile to 38.5C. Tender erythematous to violaceous subcutaneous nodules were present on the bilateral upper and lower extremities, breasts and thighs, admixed with depressed plaques. Laboratory tests revealed elevated inflammatory markers (ESR 70mm/hr (0-30mm/hr), CRP 129.4mg/L (0-10mm/hr), and ferritin 999ng/mL (50-200ng/mL)). Complete blood count revealed a normocytic anemia and lymphopenia. Comprehensive metabolic panel revealed albumin of 3.2g/dL (3.5-4.7g/dL) and AST of 51 (<41 U/L). Antibody antinuclear antibody (ANA) by ELISA was positive and ANA by indirect fluorescence negative. CT scan of the chest, abdomen and pelvis was negative for other areas of disease. Bone marrow evaluation was negative. She underwent punch biopsy.
Biopsy fixation details: Neutral buffered formalin
Frozen tissue available: none
Details of microscopic findings: H&E sections of the punch biopsy demonstrated a subcutaneous infiltrate of atypical small to medium-sized lymphocytes in association with extensive fat necrosis. Adipocyte rimming by atypical lymphocytes was prominent. Mitotic figures and karyorrhectic debris were easily identified.
Immunophenotype: The atypical lymphocytes expressed CD2, CD3, CD5 (dim), CD7, CD8 and βF1 by immunohistochemistry. CD4 highlighted admixed histiocytes. Ki67 showed a markedly elevated proliferation fraction (>80% in some areas).
Cytogenetics: none
Molecular studies: Molecular studies for TCR clonality using TCRB and TCRG BIOMED-2 primer sets were performed on paraffin shavings of the punch biopsy. TCRG and TCRB analysis demonstrates the presence of dominant clonal amplicons in multiple regions. The analyses were performed in duplicate and the results verified.
Proposed diagnosis: Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL)
Interesting feature(s) of submitted case: SPTCL is a rare subtype of non-Hodgkin lymphoma accounting for <1% of cases. The rarity of SPTCL presents a diagnostic challenge. This patient was evaluated by internists, rheumatologists, infectious disease specialists and oncologists over a three year period without a definitive diagnosis. A definitive diagnosis was rendered after appropriate sampling of the subcutaneous fat occurred. Distinguishing SPTCL, primary cutaneous gd T-cell lymphoma (gd TCL) and lupus erythematosus panniculitis (LEP) is challenging given the clinical and histological overlap of these entities; however, this exercise has important screening, management and prognostic implications. Patients diagnosed with LEP undergo evaluation for systemic lupus erythematosus and usually do well with prednisone taper and hydroxychloroquine. As exemplified in our case, SPTCL is more likely demonstrate antigen aberrancy, positive T-cell clonality studies, and increased Ki67 proliferation index compared to LEP. Separation of SPTCL from gd TCL is mainly accomplished by the demonstration of positive staining for bF1. gd TCL has high risk of hemophagocytic syndrome (HPS) and is treated with CHOP-based therapies while SPTCL generally are at lower risk for HPS and do well with prednisone taper and prolonged low dose methotrexate therapy. Our patient was treated with a three month prednisone taper and methotrexate. She has remained in remission for over 15 months on 10mg of methotrexate weekly.

EAHP18-LYWS-249

Primary cutaneous gamma delta T-cell lymphoma (PCGD-TCL) with isolated subcutaneous involvement and benign clinical course

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Case description: A 42-year-old woman presented with multiple subcutaneous nodules on her right shoulder/chest wall that had grown in size over the preceding months. She also reported fatigue and 6 pounds of unintentional weight loss. A biopsy was performed. She was treated with 6 cycles of CHOP, attaining and remaining in complete remission at her last follow-up 8 years later.
Biopsy fixation details: Multiple fragments of yellow-pink fatty tissue, fixed in formalin.
Frozen tissue available: N/A
Details of microscopic findings: Adipose tissue with fat necrosis and an extensive infiltration by lymphocytes and macrophages and rare necrotizing granulomas. Some macrophages are stuffed with apoptotic debris, focally resembling “bean bag” histiocytes. The lymphocytes are cytologically heterogeneous, with a range of small and medium-sized cells. Scattered larger and atypical forms with open chromatin, irregular nuclear contours and prominent nucleoli are noted. Multinucleated giant cells are also seen. Some rimming of the adipocytes is evident in areas, but is not a prominent finding. The septae are involved by the infiltrate. No dermal or epidermal components are present in the specimen, precluding an evaluation of involvement of these regions.
Immunophenotype: Immunohistochemical studies reveal that the bulk of the lymphoid cells are CD3+ CD5+(minor subset loss) CD43+ CD45R0+ TCRg(weak)+ T-cells that are mostly CD4- CD8-. Perforin and granzyme B are positive in a subset, particularly evident in a rimming distribution. CD1a, CD10, CD30, CD56, CD57, TCRb, TIA1, TdT, ALK, EBV-LMP1 and EBER1 are negative.
Cytogenetics: N/A
Molecular studies: TRG PCR is positive for a monoclonal rearrangement.
Proposed diagnosis: Primary cutaneous gamma delta T-cell lymphoma (PCGD-TCL)
Interesting feature(s) of submitted case: Some of the morphologic and immunophenotypic heterogeneity of this case raise an initial consideration of a reactive panniculitic process, the aggregate data are those of a T-cell lymphoma, the differential diagnosis for which includes primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL).
Features compatible with both PCGD-TCL and SPTCL

1. Multiple subcutaneous masses located in the proximal upper extremity
2. Systemic symptoms, including fatigue and 6 pounds of weight loss
3. Adipotropism with rimming of neoplastic lymphocytes around adipocytes
4. Variably prominent bean-bag histiocytes
5. Cytotoxic granule expression

Features supportive of PCGD-TCL

1. Heterogeneous lymphocytic infiltrate, rare large atypical forms, septal involvement
2. Double-negative (CD4- CD8-) T-cells
3. TCRg expression, albeit weak
4. TCRb negative

Features atypical for PCGD-TCL

1. No apparent clinical involvement of overlying skin
2. Benign clinical course; cases with subcutaneous fat involvement are even more aggressive
3. Mostly CD5+, with only minor subset loss of CD5
4. CD56 negativity

The findings in this case are overlapping between PCGD-TCL and SPTCL, but as per WHO, all cases with gamma delta expression are classified as PCGD-TCL. This case of PCGD-TCL shows isolated subcutaneous involvement and a benign clinical course. This case highlights that not all PCGD-TCL have an aggressive clinical course.

EAHP18-LYWS-259

Subcutaneous panniculitis-like T-cell lymphoma arising in a patient undergoing chemotherapy for a lymphoplasmacytic lymphoma

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Case description: A 79-year-old man undergoing chemotherapy for a lymphoplasmacytic lymphoma presented with multiple subcutaneous nodules on the arms and trunk. The clinical suspicion was that of cutaneous involvement by his known B-cell lymphoma. A deep incisional biopsy of the right upper arm lesion was performed.
Biopsy fixation details: 10% neutral buffered formalin.
Frozen tissue available: No.
Details of microscopic findings: Skin incisional biopsy including epidermis, dermis and subcutaneous fat. There is a dense lymphocytic infiltrate involving the fat lobules that comprises mostly intermediate lymphoid cells with irregular nuclear contours and inconspicuous nucleoli. Admixed with these is a population of larger atypical lymphoid cells with prominent nucleoli. There is marked rimming of the fat cells with prominent karyorrhexis. Occasional mitotic figures are present. There is limited septal involvement and sparing of the dermis and epidermis.
Immunophenotype: Immunohistochemistry shows the lymphoid cells are BF1 positive T cells co-expressing CD2, CD7 and CD8. The cells are also positive for CD3, CD5 and CD7 although with weaker intensity. Perforin, granzyme B and TIA1 are also positive. CD4 shows only patchy very weak positive staining in a proportion of the cells. CD56 is largely negative. CD30 shows only very occasional positive cells. MIB1 shows a high proliferation index. CD20, ALK1, LMP 1 and EBER-ISH are negative.
Cytogenetics: Not done.
Molecular studies: PCR showed clonal rearrangement of the TCR gamma and beta genes.
Proposed diagnosis: Subcutaneous panniculitis-like T-cell lymphoma.
Interesting feature(s) of submitted case: This case shows prominent rimming the adipocytes by the neoplastic lymphoid cells which is a characteristic feature of subcutaneous panniculitis-like T-cell lymphoma.

EAHP18-LYWS-278

Programmed cell death ligand 1 expression in primary cutaneous diffuse large B-cell lymphoma, leg type

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Case description: A 79-year-old man presented a cutaneous nodule in trunk in February 2013. The nodule was removed by surgical resection, with no more treatment. A body scan did not found other abnormally. In June 2014, he relapsed with nodules in legs. He received a treatment by rituximab and chemotherapy. He was in complete remission few months later. At last news, in April 2017, he was still in complete remission.
Biopsy fixation details: Formalin-fixed paraffin-embedded tissue.
Frozen tissue available: No.
Details of microscopic findings: Histologic examination found a dense, atypical, large-cell lymphoid proliferation, with nodular and diffuse architecture, extending in all dermis to hypodermis. Tumor cells had immunoblastic aspect. Epidermis was normal.
Immunophenotype: The lymphoid infiltrate had a B-cell phenotype with scarce CD3 or PD1 T-cells. Large tumor cells expressed BCL2, BCL6 and MUM1. CD10 was negative. Proliferation index Ki67 was high (80%). Programmed cell death ligand 1 (PD-L1) was positive within the tumor. Interestingly, double staining PD-L1/PAX5 showed that PD-L1 was expressed by PAX5 negative cells. Double immunofluorescence with antibodies against PD-L1/CD163 showed that PD-L1 was expressed by M2 macrophages which were the most abundant immune cells.
Cytogenetics: Interphase fluorescence in situ hybridization (FISH) was used to assess the status of the 9p24.1, locus encoding for PD-L1/2 with break-apart probes. A normal and balanced pattern was observed.
Molecular studies: Using an allele-specific real-time PCR technique, the $MYD88^{L265P}$ mutation was not detected.
Proposed diagnosis: We proposed the diagnosis of primary cutaneous large B-cell lymphoma, leg type (PCDLBCL-LT). Immune cells of microenvironment corresponding to M2 macrophages were responsible for an intense staining for PD-L1 within the tumor area around tumor cells.
Interesting feature(s) of submitted case: PCDLBCL-LT usually display an aggressive behavior with around 50% of relapsing/refractory cases. New therapeutic targets are needed and checkpoint molecules inhibition have been evaluated in nodal diffuse large B-cell lymphomas. Therefore, we evaluated PD-L1/2 cytogenetic alterations and PD-L1/2 expression in a series of 29 PCDLBCL-LT (Menguy et al. Am J Surg Pathol. 2017). We observed a strong PD-L1 expression within the tumor area of all interpretable cases. Double staining with PD-L1/PAX5 identified only 1 case harboring PD-L1 expression by tumor cells. All cases displayed PD-L1 expression by immune cells within tumor microenvironment. Among the whole cohort, 21/26 displayed a normal FISH pattern, 3 harbored low polysomy, and 2 harbored a rearrangement of PD-L1/2 locus. So, PD-L1 expression by M2 macrophages is a constant feature of PCDLBCL-LT. It may represent a rationale to evaluate checkpoint inhibitors, as recent data in solid tumors support that PD-L1 inhibitor may be efficient in cases with PD-L1 expression by immune cells. Our study also underscores the difficulty of differentiating PD-L1 expression by tumor cells or by macrophages using routine immunostainings.

EAHP18-LYWS-290

Primary cutaneous follicular center cell lymphoma with strong CD10 expression and 1p36 deletion

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Case description: 59 years old female with no remarkable previous clinical history. The patient consulted in January 2017 because of the presence of a deep 1 cm skin nodule below the right ear, appeared approximately 1 year before. A surgical resection of the nodule was performed. A diagnosis of primary cutaneous follicle centre cell lymphoma was favored since there were no peripheral lymphadenopathies and CT scan and peripheral blood studies were negative (bone marrow aspirate/biopsy were not performed). In November 2017, a 1.2 cm nodule appeared in the same site, without evidence of additional skin lesions, peripheral lymphadenopathy, visceromegalies or laboratory test alterations (additional staging maneuvers ongoing).
Biopsy fixation details: Formalin fixed paraffin embedded biopsy
Frozen tissue available: No
Details of microscopic findings: Both biopsies showed similar features. Morphologically, both lesions had a nodular pattern of growth with expanded germinal centers composed by a monotonous population of centrocytes and centroblasts. No diffuse areas were identified. There were approximately 9-15 centroblasts per high power field in both biopsies. The deepest resection margin of the first biopsy was minimally involved.
Immunophenotype: The immunophenotype was the same in both biopsies. The tumor cells expressed CD19 and CD20, and were bcl-2 negative or weakly positive (clones 124 and SP66, Ventana-Roche); CD21, LMO2 and bcl-6 showed the expansion of the germinal centers; CD10 was strongly expressed in both biopsies; Ki-67 was of 50%, approximately, in both samples.
Cytogenetics: FISH biopsy January 2017: no breaks or numerical alterations in IGH/BCL-2, BCL-6 and MYC; 1p36 deletion identified (in the context of non-polysomic cells)
FISH biopsy November 2017: 1p36 deletion identified (in the context of polysomic cells)
Molecular studies: IGH rearrangements of both biopsies, ongoing.
Proposed diagnosis: Primary cutaneous follicle centre cell lymphoma.
Interesting feature(s) of submitted case: This is a case of a follicular lymphoma with strong CD10 expression and 1p36 deletion involving the skin, which had a very rapid relapse. At the moment, it is considered as a primary cutaneous follicle centre cell lymphoma based on the absence of additional sites involved, morphology and phenotype. It is not known whether the depth of the tumor at presentation, isolated strong CD10 expression or 1p alterations influence the biological behavior of primary cutaneous follicle centre cell lymphoma.

EAHP18-LYWS-317

Title: Cutaneous atypical gamma delta T-cell infiltrate--primary cutaneous gamma delta T-cell lymphoma or cutaneous manifestation of hepatosplenic T-cell lymphoma?

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Case description: A 31 year old male presented to his dermatologist with bilateral rash on his lower legs. A prior biopsy was performed on 11/2017; neither the report nor slides were available for review. The patient believed his right lower leg was infected. He also reported feeling ill during the preceeding two weeks, endorsing fever, chills and night sweats. He was prescribed Kleflex and Doxycycline over the last week. Physical exam revealed areas of patchy erythema, some with admixed purpura. There were also areas of nontender, somewhat nodular erythema proximally. The right posterior calf showed superficial necrosis. A punch biopsy of the left proximal shin was performed. Laboratory studies (complete blood count, basic metabolic panel, urinalysis, erythrocyte sedimentation rate, c-reactive protein, and hepatitis serologies) were ordered, as was a chest x-ray. The patient was sent to the hospital post biopsy. There, he was found to have a low white blood cell count and low platelet count; he was also noted to have splenomegaly. No further information was available at the time of biopsy.
Biopsy fixation details: Received in 10% buffered formalin is a punch biopsy of skin measuring 4X4X5mm and 3X3X3mm. The specimen is cut into 3 pieces and entirely submitted in 2 cassettes.
Frozen tissue available: Not available.
Details of microscopic findings: There are two biopsies, one a punch specimen of skin and the other a deeper fragment of subcutaneous tissue. There is a superficial and deep perivascular and periadnexal predominantly lymphocytic infiltrate with histiocytes associated with lymphocytes involving the wall of small blood vessels and hints of perivascular and fibrin. The lymphocytes extend focally to the base of the epidermis associated with basal vacuolization, a few individual necrotic keratinocytes and increased dermal mucin. The lymphocytes are medium sized, have slightly irregular, hyperchromatic nuclei and are associated with a small amount of nuclear dust. In the deeper fragment of subcutaneous tissue there is a lobular infiltrate of predominantly lymphocytes and histiocytes. There is nuclear dust.
Immunophenotype: The lymphocytic infiltrate reacts diffusely with CD3 and CD56. CD4 highlights a subset of cells. There is a relatively small number of cells that react with CD8 and BF-1, however, the majority of the cells are negative with these markers. CD20 highlights rare cells and is negative in the infiltrate. The infiltrate is negative for CD123 and myeloperoxidase, the latter highlighting a background population of reactive cells. The infiltrate is also negative with in situ hybridization for Epstein-Barr virus. Acid fast and Fite stains are negative for mycobacteria. Immunohistochemistry for T. pallidum is negative for spirochetes. Immunostains for cytotoxic markers are not available.
Cytogenetics: Not available.
Molecular studies: Not available.
Proposed diagnosis: The proposed diagnosis is primary cutaneous gamma delta T-cell lymphoma; cutaneous involvement of undiagnosed hepatosplenic T-cell lymphoma was considered.
Interesting feature(s) of submitted case: This case highlights the differential diagnosis of gamma delta T-cell lymphomas of the skin. Clinical information, in addition to the cutaneous manifestations, can aid in the distinction between various gamma delta T-cell lymphomas involving the skin. Cytogenetic studies can also aid in the distinction. Without this information, definitive diagnosis is challenging.

EAHP18-LYWS-321

A dermatologically dubious diagnostic dilemma: Is this a primary cutaneous marginal zone lymphoma rich in TFH cells masquerading as primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder?

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Case description: A 74-year-old man with a 1 cm skin lesion on the mid upper back clinically suspicious for an inflamed nevus (submitted case). Ten months after the initial presentation, two additional small skin lesions developed and biopsies reportedly confirmed recurrence of disease (not reviewed by us). He was treated with intralesional steroid injections. One year later, a 4.5 cm plaque developed on his upper back (in the same region as the initial lesion), which was treated with localized radiation.
Biopsy fixation details: Formalin-fixed and paraffin embedded.
Frozen tissue available: No.
Details of microscopic findings: An H&E stained section reveals skin with a dense dermal lymphoid infiltrate that does not infiltrate the epidermis. Small lymphocytes with mildly irregular nuclear contours predominate with fewer scattered medium-sized cells with more open chromatin.
Immunophenotype: T-cells predominate over B-cells (~3:1). The T-cells are CD2+ CD3+ CD5+ CD43+ TCR-beta+ BCL2(var)+ with diminished CD7 expression and a CD4 bias (CD4:CD8 ratio ~8:1). PD-1 is positive in a subset (~30%) and highlights the medium sized, more atypical cells. The T-cells are negative for TCR-gamma, CD10, and BCL6. The Ki-67 proliferation index is ~5-10%. The CD20+ CD79a+ CD23(subset)+ B-cells are negative for CD5, CD10, CD43, BCL6, and CCND1. A few MUM1+ CD79a+ polytypic plasma cells are also present. CD21 and CD23 do not reveal any follicular dendritic cell (FDC) meshworks.
Cytogenetics: None.
Molecular studies: T-cell receptor gamma gene (TRG) PCR: Polyclonal rearrangements only. Immunoglobulin heavy chain gene (IGH) PCR: Monoclonal rearrangement.
Proposed diagnosis: Primary cutaneous marginal zone lymphoma (rich in TFH cells) vs a primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder
Interesting feature(s) of submitted case: This case was initially diagnosed as primary cutaneous CD4+ small/medium T-cell lymphoma (CD4SMTCL), which was recently reclassified as a “lymphoproliferative disorder” due to its indolent clinical course. However, as its name suggests, this lesion does not usually recur. The T-cells in CD4SMTCL are thought to be derived from follicular helper (FH) T-cells and typically express FH T-cell markers, such as PD-1, BCL6 and CXCL13 (but not CD10). In our case most of the medium sized more atypical cells expressed PD-1; however, they did not express BCL6 (or CD10); CXCL13 was not assessed. These cases usually have monoclonally rearranged T-cell receptor genes; but, TRG PCR in this case revealed polyclonality. In addition, a monoclonal IGH gene rearrangement was identified. While most of these cases do have a prominent B-cell infiltrate, similar to this case, a monoclonal IGH gene rearrangement has never been reported to our knowledge. The monoclonal IGH gene rearrangement could reflect a cross-lineage rearrangement in the neoplastic T-cells (with a false negative TRG PCR), or represent a prominent reactive clone that arose in response to the T-cell proliferation. However, the multiple recurrences in this patient, including a large plaque lesion, along with the monoclonal IGH gene rearrangement, suggest that this may instead be a primary cutaneous marginal zone lymphoma (PCMZL) that is rich in follicular helper T-cells. While PCMZLs may be T-cell rich, this case is perhaps exceptionally so; this, together with the absence of disrupted FDC meshworks, casts some doubt as to this diagnosis too.

EAHP18-LYWS-328

An unusual cutaneous ocular adnexal presentation of systemic anaplastic large cell lymphoma

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Case description: A 41-year-old female presented with a bump on her left eyelid that had become progressively bigger and tender over the course of 2 months. Initial biopsy was interpreted as a chalazion, but despite initial therapy with steroids and doxycycline, the lesion continued to grow from 2.5 to 4 cm over the next few weeks, eventually becoming ulcerated. The lesion was excised, and the pathology was read as anaplastic large cell lymphoma (ALCL) that was assumed to be primary cutaneous (pc) based on the absence of disease elsewhere in this otherwise asymptomatic patient. Some time thereafter, she developed fever, night sweats and a new large mass on her right thigh. Biopsy of the mass (not available for review) revealed ALCL. CT showed a splenic mass and splenic and right pelvic adenopathy. In light of the new findings, the original diagnosis of pcALCL was revised to systemic ALCL with secondary cutaneous involvement. The patient received etoposide-CHOP therapy.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: H&E stained sections of the eyelid lesion reveal dermal expansion by a dense and diffuse population of small to markedly large, pleomorphic cells with round to highly irregular nuclear contours, dispersed chromatin and variably prominent nucleoli that are occasionally eosinophilic and inclusion-like. Many of the large cells resemble “hallmark” cells with multilobated, horseshoe- and wreath-like nuclei. Heightened mitotic activity with frequent atypical mitoses is noted.
Immunophenotype: The neoplastic cells are predominantly positive for CD2, CD4 (dim), CD5, CD30, perforin, and MUM1 with Ki67 positive in ~80%. CD3, CD45 and Granzyme B are positive in a minor subset of neoplastic cells. Stains for PAX5, CD7, CD8, CD15, CD20, CD56, CD57, CD279, EBER1, ALK, TIA1, TCR-beta, TCR-gamma, S100, Melan A, and PanCK are all negative.
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Systemic anaplastic large cell lymphoma, ALK-negative, with secondary cutaneous involvement
Interesting feature(s) of submitted case: This case illustrates an extremely rare and unusual presentation of systemic ALCL with secondary cutaneous involvement of the eyelid, which was initially interpreted to reflect pcALCL.

Ocular adnexal lymphomas are rare, accounting for <2% of lymphomas and <8% of extranodal lymphomas, with lymphomas of the eyelid comprising a minor subset of these cases (5%). ALCL constitutes only 2% of eyelid lymphomas (4 reported cases to date).

This case is also unusual in that systemic disease is typically evident in systemic ALCL at the time of diagnosis; however, in this case, the systemic manifestations only became evident subsequently.

This highly aggressive ALCL along with the less aggressive pcALCL and the clinically indolent lymphomatoid papulosis make up a spectrum of cutaneous CD30+ T-cell lymphoproliferative diseases. As these rare entities can demonstrate histologic (and sometimes clinical) overlap but differ vastly in prognosis and management, distinguishing the different diseases is crucial yet also very challenging on purely pathologic grounds. Transformed mycosis fungoides is also in the pathologic differential diagnosis.

EAHP18-LYWS-335

CD4/CD8/CD30 positive buccal peripheral T-cell lymphoma, NOS

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Case description: 86 year-old woman presented with lesions in the mouth that began 2 months prior to presentation. Lesions have been persistent for the past 2 months and have worsened and caused pain. She lost some weight (~2lbs/week) due to difficulty eating. Her PMH is significant for HTN, osteoarthritis and hypothyroidism. On physical examination there is a lesion on the mucosal surface near the lip that involves swelling and ulceration. Clinical differential diagnosis was lymphoma, deep fungal infection, traumatic ulcerative granuloma with eosinophilia, granulomatous lesion.
Incisional biopsy was performed for further evaluation
Biopsy fixation details: The biopsy specimen was fixed in formalin.
Frozen tissue available: No.
Details of microscopic findings: H&E stained sections show squamous mucosa with a diffuse submucosal infiltrate composed of predominantly large atypical cells with oval and irregular nuclei, dispersed chromatin, prominent nucleoli and scant cytoplasm. Increased scattered and focally also clustered eosinophils are present. Mitotic figures are easy to identify. Areas of ulceration and necrosis are present.
Immunophenotype: Immunostains are performed with adequate controls and show the neoplastic cells are CD45+ CD2+ CD3+ CD5(sub dim)+ CD7(sub dim)+ CD4+ CD8+ CD30(diffuse bright)+ MUM1(subset)+ BCL2(dim var)+ cMYC(var)+ Perforin+ TIA1+ granzymeB+ TCR-BF1+ and TCR-G- BCL6- cyclinD1- TdT- CD1a-(only stains scattered dendritic cells) CD56- CD57- ALK- S100- and panCK-. Ki67 labels 60-70% of the cells. CD34 highlights background vessels. CD10 is difficult to interpret due to background staining. PAX5 stains a few scattered small B cells. An EBER(ish) is negative. Flow cytometry studies were non-diagnostic.
Cytogenetics: Not performed.
Molecular studies: A monoclonal T cell receptor (TCR) gamma gene rearrangement was identified in the submitted buccal mucosa specimen and showed a ~215 bp peak in Vgamma 1-8 reaction.
Proposed diagnosis: Peripheral T-cell lymphoma, NOS
Interesting feature(s) of submitted case: -Positivity for CD30
-Double expression of CD4 and CD8
-Expression of cytotoxic markers
-Rare localization to buccal mucosa
-Limitation of the disease to oral cavity
-Positivity for cMYC

EAHP18-LYWS-336

Cutaneous CD8+ peripheral T-cell lymphoma, NOS with an activated cytotoxic phenotype

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Case description: 35-year-old man presented with fever and upper respiratory infection (URI) symptoms. He had a 7-8 moths history of central facial edema, migratory subcutaneous nodules (most prominent on his forehead and upper lip) without overlying epidermal change, photophobia, eye pain and discharge, skin itching and rash (migratory in trunk and extremities), intermittent night sweats and a 20 pound weight loss. He also has a PMH of seasonal allergies. Physical examination revealed subcutaneous lesions on his face and periorbital and facial edema, right eye discharge and cervical LAD. His respiratory symptoms quickly resolved with oral antibiotics. Clinical differential diagnosis was infectious vs. lipoma vs. lymphoma vs. other. PET-CT revealed multiple FDG avid foci involving the skin and soft tissues of the face suggestive of hypermetabolic malignancy. No solid organ involvement was noted on PET-CT. MRI of the orbits revealed preseptal swelling involving left and right eye but no evidence of brain involvement. Punch biopsy of the left forehead skin was performed for further evaluation.
Biopsy fixation details: The biopsy specimen was fixed in formalin.
Frozen tissue available: No.
Details of microscopic findings: H&E sections show a dense subcutaneous infiltrate of lymphoid cells with oval to angulated irregular nuclear contours, moderately condensed chromatin and scant cytoplasm, admixed with histiocytes and a small population of small lymphocytes; scattered mitotic figures and rare eosinophils are seen. There is increased interstitial mucin in the panniculus.
Immunophenotype: Immunohistochemical staining performed with adequate controls show that the lymphocytic infiltrate is composed predominantly of CD2, CD3, CD7, CD8, perforin, granzyme, and TCR alpha-beta positive T cells with subset loss of expression of CD5 and are negative for CD1a, CD30, CD56, ALK1 and EBER(ish). Staining for TIA1 was suboptimal, with high background precluding definitive evaluation. A few T cells are positive for CD57, TCR gamma and TCR delta. CD4 is positive in a few T-lymphocytes and mainly stains scattered macrophages. CD20 and CD79a stain rare B-lymphocytes and a few plasma cells. CD68 stains diffusely scattered macrophages. The Ki67 proliferative index is approximately 30% in the atypical T cell population.
Cytogenetics: Not performed.
Molecular studies: A monoclonal T cell receptor (TCR) gamma gene rearrangement is identified in the peripheral blood specimen. A prominent 212 bp peak in polyclonal distribution was seen in the Vgamma 1-8 reaction and a prominent 179 bp peak in polyclonal distribution was seen in the Vgamma 9-11 reaction.
Proposed diagnosis: Cutanous CD8+ peripheral T-cell lymphoma, NOS with an activated cytotoxic phenotype.
Interesting feature(s) of submitted case: The combined findings are those of a peripheral CD8+ T cell lymphoma with an activated cytotoxic phenotype, not otherwise specified. Although a few activated appearing gamma delta T cells are seen, the vast majority of the T cells (and those that appear to have subset loss of CD5 expression) are alpha beta T cells, strongly favoring that this is a T alpha beta neoplasm. This lesion is located in subcutaneous tissue and the epidermotropism characteristic of a primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphoma is not appreciated in this specimen. Also arguing against this more aggressive CD8+ T cell lymphoma is the low proliferative rate, and the reported relatively indolent clinical behavior. This lesion is favored to represent a less aggressive neoplasm, similar to primary cutaneous acral CD8+ T-cell lymphoma predominantly described on the ears.

EAHP18-LYWS-360

Primary cutaneous γδ-T cell lymphoma with subcutaneous panniculitis-like features

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Case description: The patient is a 41 years-old woman who is admitted with multiple bullae and crusted wounds on her skin throughout the whole body, mostly in her legs for a month. The white cell count in blood was low ($2.9x10^9$/L, N: $4.5\text{-}11x10^9$). She had weight lost about 3-4 kg and night fevers. LDH was high (843 U/L, N: 0-248 U/L). She had no lymphadenopathy or hepatosplenomegaly. Skin biopsy from leg was performed. After the diagnosis of primary cutaneous lymphoma, bone marrow biopsy was carried out and no involvement was found. The patient had received only one cure of chemotherapy and steroid. However, she died 5 months after the diagnosis caused by infectious pneumonia and hemodynamic disorders.
Biopsy fixation details: Formalin fixed paraffin embedded tissues
Frozen tissue available: No.
Details of microscopic findings: In the skin biopsy taken from the leg, beneath the spongiotic epidermis, there was a lymphohistiocytic dermal infiltrate showing condensation around the vessels and skin appendages. There were minimal epidermotropic neoplastic individual cells between keratinocytes. The infiltration was spreading to subcutaneous fat tissue creating "rimming" around the fat lobules. Presence of many phagocytic histiocytes containing apoptotic bodies was remarkable. In some areas, neoplastic cells were accompanied by mucinous material. A few small vessels with angiodestruction caused by infiltration of neoplastic cells were seen. Neoplastic lymphocytes had middle size nuclei with irregular borders. There were also single large cells or cells with smaller nuclei. Mitotic figures were frank.
Immunophenotype: The neoplastic cells were positive by CD3, CD2, cytotoxic markers (TİA, perforin, granzyme), CD56, whereas βF1, CD5, CD7, CD4, and CD8 were negative. The other negative markers were CD25, CD20, CD57, CD30, CD16, PD-1, CD10, bcl-6 (10%, weakly), CD1a, and EBER. Ki-67 was 70% in the neoplastic cells.
Cytogenetics: Not done.
Molecular studies: Not done.
Proposed diagnosis: Primary cutaneous γδ-T cell lymphoma
Interesting feature(s) of submitted case: The patient has and aggressive and rare primary cutaneous T-cell lymphoma showing subcutaneous panniculitis-like lymphoma-like histopathological features.

EAHP18-LYWS-371

CNS involvement on relapse of cutaneous anaplastic large cell lymphoma

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Case description: A 63-year-old Caucasian male developed erythematous skin lesions on his left forearm. A skin biopsy showed ALK-negative anaplastic large cell lymphoma (ALCL). No other sites of disease were detected on imaging. The patient was treated with local radiotherapy. Two years later, he presented to our institution with aphasia. Brain imaging revealed enhancing lesions in the left frontal and right parietal cerebral cortex. A brain biopsy revealed involvement by ALK-negative ALCL. Repeat whole body imaging showed no other sites of involvement. Bone marrow (BM) was not involved. Multiple erythematous skin lesions following the brain biopsy were biopsied, with one biopsy showing persistent/relapsed disease. He was treated with systemic chemotherapy and autologous stem cell transplant. His post-transplant course was complicated by mucositis, engraftment syndrome, and worsening of erythematous skin rashes. He died about a year after relapse of the lymphoma in the brain.
Biopsy fixation details: Brain and skin biopsies were fixed in formalin. BM biopsy fixed in Bouin's solution. Fresh tissue for flow cytometric, cytogenetic and molecular analysis.
Frozen tissue available: None
Details of microscopic findings: The skin biopsy showed a dense nodular dermal infiltrate of large pleomorphic lymphocytes with anaplastic morphology and brisk mitoses. No epidermotropism was seen.
The brain biopsy showed a diffuse infiltrate of medium to large pleomorphic lymphocytes with round to irregular nuclei, coarse chromatin, indistinct to small nucleoli and moderate cytoplasm, associated with brisk mitotic activity and apoptotic debris.
Immunophenotype: By IHC (of the brain and skin biopsies), the cells were positive for CD3, CD8, CD2, CD30, CD25, BCL6, MUM1, granzyme B, and TIA1; and negative for CD20, CD4, CD56, CD5, CD7, CD10, ALK1, TCR-gamma, PD1, p63, and EBER (ISH). Ki-67 showed a proliferation index of >90%.
Flow cytometry of the brain lesion showed cytoplasmic CD3+, surface CD3-, surface TCR negative, CD8+, CD2+, CD25+, CD30+, HLA-DR+, CD56-, CD4-, CD5-, CD7-, CD43-, CD103-, CD19-, CD20-, and CD10- lymphocytes.
Cytogenetics: FISH analysis of the brain lesion using the DUSP22-IRF4 break-apart probe, showed 5 copies of DUSP22-IRF4 and 3 copies of chromosome 6 centromere, findings indicative of trisomy 6 and duplication 6p. No DUSP22 or IRF4 rearrangements were detected.
Molecular studies: PCR analysis for TCRβ gene rearrangement of the brain and skin lesions showed clonal products of the same size indicating clonally related lymphoid populations.
Proposed diagnosis: CNS relapse of cutaneous ALCL (CD30+/CD8+/ALK1-negative cytotoxic T-cell phenotype)
Interesting feature(s) of submitted case: The primary skin presentation with negative imaging studies was consistent with a primary cutaneous ALCL (pcALCL). The cytotoxic CD8+ phenotype is less common in this disease. Rare cases of primary CNS ALCL and CNS involvement by systemic ALCL have been reported. Extra-cutaneous dissemination occurs in about 10% of pcALCL, mainly involving the regional lymph nodes. CNS relapse 2 years after initial diagnosis of pcALCL is very unusual and unique feature of this case. No well documented cases reporting this phenomenon have been reported. Cytogenetic findings revealed a duplication involving the DUSP22-IRF4 region on chromosome 6p, but no rearrangements were seen. Absence of p63 expression would rule out p63 rearrangements ("triple-negative" ALCL). Patients with pcALCL, including those with regional nodal involvement have a favorable prognosis. Owing to the lack of pcALCL cases with CNS involvement, the prognosis of such patients is unclear.

EAHP18-LYWS-398

Young female with Primary cutaneous anaplastic large-cell lymphoma. Case report.

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Case description: Introduction.
Primary cutaneous anaplastic large-cell lymphoma (PCALCL) is included in the group of CD30+ primary cutaneous lymphoproliferative disorders (LPD). Usually, clinical diagnosis is difficult because of various manifestation of recurrent spontaneously healing lesions to ulcerations. Mostly, it occurs people near 60 years old with the male to female ratio 1.5-3 to 1, respectively. Treatment algorithms dependent on clinical stage and varied from clinical monitoring and radiation therapy and/or surgical excision to systemic chemotherapy.
Patient's History.
A 32-year-old female presented to Oncohematology department of National Cancer Institute (Kiev, Ukraine) in 12/2017. She complained about small blemishes on the skin of upper and low extremities which primarily she observed in 08/2017.
This blemishes spontaneously appeared and disappeared from time to time without symptoms. In the middle of November, she noted growing itching plaque with ulceration on the inside part of the right elbow joint. She asked a dermatologist for consultation after what biopsy of this formation had been done. Biopsy results confirmed PCALCL.
There was no history of generalized weakness, weight loss, fever
The patient does not have any past medical history and no current medications in use.
Physical examination.
After evaluation of all blemishes on the body, we found 5 small formations on the upper and 3 on the lower extremities. The diameter of hyperpigmentation blemishes is not more than 0.7 mm - 1.0 sm and they are light-pink-brown color, asymptomatic. The larger lesion, which is near 3x5 sm in diameter, presented as a plaque with itching and ulceration of the right elbow joint. Any other similar lesions were observed. Systemic physical examination showed no abnormalities and peripheral lymph nodes enlargement.
Laboratory data.
Peripheral blood analysis and biochemistry were normal. The whole body CT-scan showed any abnormalities and lymph nodes enlargement.
Treatment.
The therapeutic strategy was chosen in favor of radiation therapy (RT) to an ulcerated lesion, locally. Systemic corticosteroids and antihistamine treatment were used to resolve itching. After 4 cycles patient responded well to RT. An obvious result was demonstrated after 7 cycles of RT. This therapeutic option showed a significant improvement and now we are waiting to the end of RT. Other asymptomatic skin blemishes, previously described, are under follow-up.
Biopsy fixation details: For biopsy fixation, we used standard 10% neutral buffered formalin (NBF).

Frozen tissue available: Frozen tissue has not been done.
Details of microscopic findings: In the biopsy material, there are skin fragments with diffuse infiltration by elements of malignant lymphoma. The tumor showed a diffuse growth with polymorphic abnormally shaped nuclei, with light eosinophilic cytoplasm, high epidermotropism, and presence of necrosis.
Immunophenotype: The activation antigen CD30 is positive in 90% of tumor cells. Tumor cells are also positive with CD2, CD4 and negative with CD3, CD8, and CD246 (ALK).
Cytogenetics: Cytogenetics has not been done.
Molecular studies: Molecular studies have not been done.
Proposed diagnosis: Primary cutaneous anaplastic large-cell lymphoma without systemic involvement, stage IE (Ann Arbor) and T1b N0 M0 B0 (TNM).
Interesting feature(s) of submitted case: The present case report is interesting because of presentation in the young age (it occurs people near 60 years old) with spontaneous regression without any active symptoms till becoming persistent by clinical progression. As well as, here we can observe very high expression of activation antigen CD30 (more than 90%).

EAHP18-LYWS-399

Parallel evolution of lymphomatoid papulosis and refractory systemic diffuse large B-cell lymphoma: 8 years follow-up

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Case description: A 57 year-old man presented in 2010 with papular cutaneous tumors, followed in 2012 and 2013 by other similar cutaneous lesions with spontaneous regression, evocative of lymphomatoid papulosis (LyP) (no biopsy available). In 2013: cervical lymph node tumor evocative of diffuse large B-cell lymphoma (DLBCL). In May 2014: cutaneous LyP papules of the arm. In Sept 2014: DLBCL relapse involving sus-clavicular lymph nodes. In Dec 2014: multiple cutaneous LyP papules with 2 larger nodular lesions of the thigh and wrist (1,5 cm in diameter) suspicious of cutaneous anaplastic large cell lymphoma (c-ALCL). In Sept 2015: inguinal lymph node tumor evocative of secondary diffusion of c-ALCL/LyP. In Jan and Nov 2016: 2 sequential DLCL relapses in cervical lymph nodes. From Dec 2016 to Jan 2017: multiple LyP papules of the legs and elbows. In Jan 2018: Complete remission after allogenic bone marrow transplantation.
Biopsy fixation details: 4% formalin.
Frozen tissue available: No (used for molecular analyses).
Details of microscopic findings: The different cutaneous CD30+ lesions were either type A LyP with few CD30+ large cells admixed with numerous reactive T-cells (May 2014) or type C LyP (Dec 2014 and 2017) with sheets of large CD30+ cells with polylobated or reniform nuclei. The latter pattern was also observed in the 2 lesions clinically suspicious of c-ALCL. No significant epidermotropism was observed. The 2015 lymph node was involved by an ALCL-like proliferation characterized by diffuse sheets of CD30+ large cells, including hall-mark cells. The different DLBCL lesions exhibited common classical features including sheets of large immunoblastic or centroblastic cells.
Immunophenotype: CD30+ large cells in LyP and c-ALCL lesions were CD20-/ ALK1 - and occasionally expressed T-cell markers like CD43, CD2 and CD8 (negativity of CD3, CD4, CD5, CD7). The ALCL-like lymph node tumor was EMA+ and negative for T-cell markers (except CD43+). DLBCL tumors were uniformly CD20+/CD30-/CD3-
Cytogenetics: DLBCL tumors all had BCL6 rearrangement evidenced by FISH (not found in LyP lesions).
Molecular studies: Clonality: Common IgH gene rearrangement of 280 bp found in the 4 analyzed DLCL relapses (suggesting common clonal B-cell origin), with polyclonal TCR. A common TCR rearrangement of 263 bp found in the 4 analyzed CD30+ sequential lesions, including LyP and ALCL-like lymph node tumor (suggesting common clonal T-cell origin), with polyclonal IgH.
Array CGH and targeted NGS: the 4 analyzed DLCL tumors shared common genomic abnormalities, with limited number of private alterations which dramatically accumulated in the most recent tumor (late divergence). In contrast, the 3 analyzed sequential CD30+ lesions showed rare mutations and copy number alterations which were mostly private (early divergence) and included 4q and 22q13 deletions containing the PRDM8 and TIMP3 tumor suppressor genes, respectively.
Proposed diagnosis: LyP complicated by c-ALCL with lymph node diffusion and associated with refractory DLBCL
Interesting feature(s) of submitted case: - In this exceptional case (previously not described association of DLBCL and LyP), B-cell tumors and LyP lesions are clonally unrelated. -Clonal evolution of sequential LyP/c-ALCL lesions has not been previously reported. - Multiple cutaneous and lymph node localizations of LyP/c-ALCL are clonally related, originating from a common precursor with early divergence. -LyP tumors exhibit a relative genomic stability over time (when compared to DLCL evolution).

EAHP18-LYWS-400

Subcutaneous Panniculitis-like T-cell Lymphoma

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Case description: A 55-year-old female presented to the University of Alabama at Birmingham (UAB) Hospital with a medical history of cutaneous T-cell lymphoma (CTCL), status post chlorambucil therapy, in full clinical remission. She did not have any other medical conditions, i.e. autoimmune diseases. She developed multiple subcutaneous nodules in bilateral upper arms and left lower outer quadrant breast. She was treated with long-term prednisone and is currently in full remission.
Biopsy fixation details: Excisional skin biopsies were obtained from the right and left arms. The biopsies were fixed in formalin, embedded in paraffin, and 4µ thick sections were mounted and stained using routine hematoxylin & eosin stain.
Frozen tissue available: Not performed.
Details of microscopic findings: Unremarkable epidermis with dense atypical lymphoid infiltrate in the subcutaneous adipose tissue and some in the dermis. The lymphoid infiltrate is characterized by small to medium sized lymphocytes containing a rim of pale basophilic cytoplasm and slightly irregular, hyperchromatic nuclei. The abnormal lymphoid infiltrate is most prominent in the subcutaneous adipose tissue where it displays rimming of individual adipocytes. The lymphomas cells also invade surrounding blood vessels.
Immunophenotype: Flow cytometry: Flow cytometry analysis shows an atypical lymphoid infiltrate of immature T-cells that are CD3+ with a predominance of CD8+ subtype.
Immunohistochemistry: The lymphoma cells were positive for CD3, CD7, and CD8 as well as Granzyme B and were negative for CD4, CD5, CD30, CD56, and CD57. The histiocytes focally rimming the adipocytes expressed CD4.
In-situ hybridization for EBER was negative.
Cytogenetics: Not performed.
Molecular studies: Polymerase chain reaction for T-cell receptor gamma and beta gene rearrangement (TCRG and TCRB) was performed. The TCRB gene showed multiple prominent peaks at 190, 263, and 266. These were significant elevations compared to the control sample but seen in the background of a polyclonal population of TCR gene rearrangement products. These findings although abnormal did not definitively define a monoclonal T-cell population and were interoperated as intermediate results.
Proposed diagnosis: Subcutaneous panniculitis-like T-cell lymphoma.
Interesting feature(s) of submitted case: The present case is a rare type of T cell lymphoma with clinical and diagnostic challenges for the clinicians and pathologists. The disease usually presents with multiple subcutaneous nodules mostly involving the extremities. SPTCL is a frequent mimicker of benign conditions, such as lupus panniculitis (LP), and may pose a significant diagnostic challenge, particularly in small punch biopsies. LP often involves dermis and subcutis with rimming of the adipocytes. The majority of cases have a lymphoid infiltrate along with other chronic inflammatory cells including plasma cells, which is not a common feature in SPTCL. Also, reactive lymphoid follicles can be seen in LP and not in SPTCL. The current case interestingly did not show definitive rearrangement of TR genes, which can potentially be problematic when differentiating from benign mimickers. However, the characteristic morphologic and immunophenotypic features and patient's past medical history of CTCL responding to chemotherapy are consistent with a diagnosis of SPTCL.

EAHP18-LYWS-430

Primary cutaneous follicle centre lymphoma with BCL2 rearrangement

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Case description: A 75-year-old female presented with a lump on the vertex of her scalp which had been growing slowly over the previous year. The lump was biopsied and a diagnosis of lymphoma made. CT scans of chest, abdomen and pelvis showed no disease elsewhere. Bone marrow biopsy was not performed. She was treated with radiotherapy to the scalp (30Gy over 22 days) with complete remission of the lump. Eighteen months later the patient presented with a two-month history of a small erythematous raised lesion on her posterior scalp. Biopsy confirmed relapse but re-staging with CT scan showed no extracutaneous dissemination. The patient was not keen to undergo further radiotherapy so wide excision of the lesion was performed. At last review, 48 months after initial diagnosis, and 18 months after excision of relapse, the patient was alive with no evidence of disease.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: The presenting biopsy and relapse biopsies showed similar features. A dense lymphoid infiltrate with a follicular growth pattern is present in the dermis and extends into the subcutis. The follicles are of relatively uniform size and closely packed. They comprise a majority of centrocytes with relatively few centroblasts. There is no zonation and mantles are absent.
Immunophenotype: The follicle centre cells and a significant proportion of interfollicular lymphocytes are of B-lineage with the following aberrant phenotype:
Positive: CD10, CD20, BCL6, BCL2 (strong uniform)
Negative: CD3, CD5, IRF4, Cyclin D1
Ki67 index: variable, overall 20-30%
Cytogenetics: Not done
Molecular studies: A BCL2/IGH translocation was demonstrated by FISH. PCR studies for t(14;18) are pending.
Proposed diagnosis: PRIMARY CUTABNOEUS FOLLICLE CENTRE LYMPHOMA (BCL2 protein positive with BCL2 rearrangement)
Interesting feature(s) of submitted case: Primary cutaneous follicle centre lymphoma (PCFCL) is a tumour of neoplastic follicle centre cells which are reported to typically lack, or show only weak BCL2 expression and to rarely harbour BCL2 rearrangements. PCFCL is considered distinct from nodal follicular lymphoma (FL) which may also involve the skin during disease dissemination, and the presence of strong BCL2 expression or a BCL2 rearrangement is said to favour the latter. However, the very low incidence of t(14;18) historically reported for PCFCL is based largely on PCR studies. Analysis by FISH is much more sensitive and recent reports have documented BCL2 gene rearrangements in up to 45% of cases. The current case shows pathological features indistinguishable from those seen in FL, and is primarily classified as PCFCL on the basis of its origin in, and restriction to, the skin. This case emphasizes that BCL2 expression and presence or absence of BCL2 rearrangement should not be used as a surrogate for thorough staging studies. It also raises the possibility that at least some PCFCL may be more closely related to FL than currently promulgated as well as interesting questions as to why t(14;18)(q32;q21) escapes detection in PCFCL harbouring BCL2 rearrangements detectable by FISH.

EAHP18-LYWS-466

Lymphomatoid papulosis, type D: A Diagnostically Difficult Dermatologic Disorder

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Case description: A 53-year-old man developed a cluster of papules on his right thigh over the course of 10 weeks. An extramural biopsy (#1) was read as CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8AECTCL) and then submitted to us in consultation. One month later he was seen at our hospital where repeat biopsies (#2A and #2B) were performed. At follow-up one month later, he showed partial spontaneous resolution of the right thigh papules and new papules on his left forearm, which were biopsied (#3). The original diagnosis was revised to lymphomatoid papulosis, type D (LyP-D). One year after initial presentation, patches developed on his shoulder and hip that were diagnosed as mycosis fungoides (MF). Over the next seven years, he had >10 self-resolving outbreaks of LyP-D on his trunk and extremities and mostly stable MF, treated with topical steroids and phototherapy.

Biopsy fixation details: Formalin

Frozen tissue available: No

Details of microscopic findings: H&E stained sections (#1) show a skin biopsy with a band-like lymphocytic infiltrate at the dermal-epidermal junction with exocytosis of lymphocytes into the epidermis. The epidermal lymphocytes are mostly medium-sized with hyperchromatic, pleomorphic nuclei. This is associated with a superficial and mid-dermal perivascular infiltrate of smaller lymphocytes with less atypia. Psoriasiform epidermal hyperplasia and parakeratosis, but no ulceration, necrosis or microabcesses, is seen. Repeat biopsies (#2A, #2B, and #3) show similar features.

Immunophenotype: #1: There were immunohistochemical differences between the epidermal and dermal lymphocytes:

Epidermal:

- Positive: CD2, CD3, CD5(dim), CD8, CD30(subset), CD45
- Negative: CD4, CD7, CD45RO, TIA-1

Dermal:

- Positive: CD2, CD3, CD4, CD5, CD7(subset), CD45, CD45RO
- Negative: CD8, CD30, TIA-1

Cytogenetics: Not performed

Molecular studies: TRG PCR:

Right thigh (#1)

- Vg1-8: 235 bp peak
- Vg9-11: 190 bp doublet peak

Right thigh medial (#2A)

- Vg1-8: Polyclonal
- Vg9-11: 176 bp peak in polyclonal background

Right thigh lateral (#2B)

- Vg1-8: 235 bp peak in polyclonal distribution
- Vg9-11: 176 bp peak in polyclonal background

Proposed diagnosis: Lymphomatoid papulosis, type D

Interesting feature(s) of submitted case:

- This case was originally submitted with an extramural diagnosis of CD8AECTCL, which may be pathologically indistinguishable from LyP-D, but, unlike LyP-D, is characterized by an aggressive clinical course. Also in the differential at initial presentation was clinically indolent CD8+ mycosis fungoides. As time revealed the self-limited waxing and waning nature of the lesions, the diagnosis of LyP-D became apparent.
- The neoplastic (epidermal) component and reactive (dermal) component showed distinct cytologic and immunophenotypic differences.
- Our case showed a non-prototypic immunophenotype. While CD30 (90% of cases) and at least one cytotoxic marker (TIA-1, granzyme B) are typically expressed in LyP-D, our case was negative for TIA-1 and only showed subset positivity for CD30.
- Monoclonal TRG rearrangements were identified in all biopsies. Identically sized peaks (235 bp, Vg1-8) were seen in biopsy #1 and #2B, suggesting a related process. While biopsy #2A was negative for this peak, biopsy #2A and #2B shared an additional identically sized peak (176bp, Vg9-11 primers).
- The patient subsequently developed CD8+ MF a year after his initial presentation; however, this did not show the dominant monoclonal rearrangements seen in the LyP-D.

EAHP18-LYWS-488

A primary indolent CD8 lymphoma of the left foot

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Case description: 82-year-old caucasian woman who presented in january 2012 a lesion situated on the left heel She had a medical history of HBP, a treated syphilis, and a recurrent infection by HSV. Her only treatment was for control her blood pressure. She was hairdresser and did not show alcoholic or tobacco intoxication. It was an erythematous, keratotic, isolated lesion which evolved for two years. This lesion was well demarcated and was indolent. In the meantime, a work-up for spread has been performed (abdominal echography and thoracic radiography) and confirmed the isolated character of this lesion.
Biopsy fixation details: 4% buffered formol, then embedded in paraffin
Frozen tissue available: yes
Details of microscopic findings: under the microscope, we observed a dense non epidermotropic lymphoid infiltrate in the most part of the dermis with extension to the hypodermis. The epidermis was normal. Cytologically, the infiltrate consisted of monomorph atypical lymphoid cells of medium size with mitosis. The reactional lymphocytes with small nucleus were few. And there wasn't no another cells. There was no vascular alteration.
Immunophenotype: The immunohistochemical study showed that those cells were CD3 + CD4- CD5 + CD7- CD8+.
The TiA1 was the only positive cytotoxic factor (granzyme B and perforin were negative).
There weren't any associated CD20 + B cells and no expression of CD30 or CD56.
The EBER RNA by in situ hybridization technique wasn't overexpressed.
The ki67 expression was about 10% of the cells.
On the frozen sections, we showed expression of TCRalpha/beta (only few gamma/delta reactional cells).
Cytogenetics: N/A
Molecular studies: A study of lymphocyte clonality was performed by PCR showing a monoclonal T proliferation.
Proposed diagnosis: indolent CD8 T lymphoma
Interesting feature(s) of submitted case: We report a new case of this rare cutaneous lymphoma described in 2008 usually located on the face. It is an emerging entity characterized clinically by slowly enlarging papules and nodules consistant of clonal nonepidermotropic medium-sized atypical CD8(+) T-cells. Although majority of lesions are solitary and located on the ears, bilateral symmetrical presentations as well as acral sites have been described.
First of all, this case is rare because of its localisation, wich hasn't been ever described.
More over, this case allows to discuss about the differential diagnosis of this lesion, which are important to know because of his prognostic which is well better than all the other differential diagnosis.
Indeed, the histological differential diagnosis consist on primary cutaneous aggressive epidermotropic CD8+ T-cell Lymphoma, CD8+ Mycosis Fongoid, or gamma/delta T lymphoma.
On this case, the pathogical and clinical confrontation suggested an indolent lymphoma and was against a CD8 + Mycosis Fongoide . The TCR alpha/beta expression didn't agree with gamma-delta CD8 + T lymphoma. The absence of epidermopism and clinical evolution were against à epidermotropis aggressive CD8+ lymphoma.
The final diagnosis was indolent CD8+ T lymphoma.
No therapy was instituted and the patient is under medical supervision since 2012, without other new lesions.

EAHP18-LYWS-505

Primary cutaneous follicle center lymphoma in a 64-year-old man

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Case description: A 64-year-old man first presented with a 3cm erythematous nodule on his left chest, which was biopsied and diagnosed as primary cutaneous follicle center lymphoma. One year later after completion of radiation treatment, he presented with a 4cm indurated, erythematous chest lesion at the site of prior treatment.
Biopsy fixation details: Formalin-fixed, paraffin-embedded tissue
Frozen tissue available: None
Details of microscopic findings: The specimen consists of skin and subcutaneous tissue with an atypical lymphoid infiltrate consisting of small-to-large perivascular nodular aggregates of lymphoid cells involving superficial and deep dermis without involvement of the epidermis. Some areas of the infiltrate have a diffuse architecture. The infiltrate consists of small centrocytes with scant-to-moderate cytoplasm and irregular nuclei with clumped chromatin, interspersed with medium-sized-to-large centrocytes with moderate amounts of cytoplasm and irregular nuclei with vesicular chromatin. There are admixed small, mature lymphocytes.
Immunophenotype: Immunohistochemical stains show that the nodular lymphoid aggregates consist of CD20+ BCL6+, MUM1- B cells with faint BCL2 expression in a small subset of the population. CD10 is faintly expressed in follicular areas, and absent in areas of diffuse growth. A stain for CD21 shows does not highlight follicular dendritic cell meshworks in either follicular or diffuse areas. Ki67 shows moderate proliferative activity. There are many admixed small mature CD3+ CD5+ T cells with unremarkable CD4:CD8 ratio.
Cytogenetics: FISH for BCL2 and BCL6 gene rearrangements will be performed for presentation.
Molecular studies: Targeted next-generation sequencing was performed and showed an absence of mutations in epigenetic modifier genes characteristically mutated in typical follicular lymphoma (EP300, CREBBP, EZH2, KMT2D, ARID1A). Mutations were also not identified in genes commonly mutated in pediatric-type follicular lymphoma such as TNFRSF14, MAP2K1, MAPK1, or IRF8.
Proposed diagnosis: Primary cutaneous follicle center lymphoma
Interesting feature(s) of submitted case: This is a classic case of primary cutaneous follicle center lymphoma. The case shows the variation of CD10 expression that can be seen in primary cutaneous follicular lymphoma. Mutational analysis suggests the possibility of biological differences between the current case of primary cutaneous follicle center lymphoma and systemic typical follicular lymphoma.

EAHP18-LYWS-510

An elderly woman with primary cutaneous diffuse large B-cell lymphoma, leg type

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Case description: An 89-year-old woman who was previously diagnosed with CLL (bruising, anemia, thrombocytopenia) noted a red spot on her ankle, which grew and persisted after treatment of CLL with bendamustine/rituximab and resolution of CLL-related symptoms. Staging studies showed that her disease was confined to the leg. Flow cytometry of the peripheral blood has been negative since initial treatment for CLL. Biopsy of the leg lesion was performed.
Biopsy fixation details: Formalin-fixed paraffin-embedded tissue sections
Frozen tissue available: None
Details of microscopic findings: Microscopic sections show a dense non-epidermotropic dermal infiltrate of large neoplastic lymphocytes with irregular ovoid nuclei, slightly open chromatin, prominent nucleoli, and moderate amounts of amphophilic cytoplasm. There are admixed small lymphocytes, histiocytes and plasma cells. Scattered mitoses and apoptotic debris are seen.
Immunophenotype: Immunohistochemical stains show that the neoplastic cells are PAX5+ B-cells that co-express MUM1, BCL2 (strong), BCL6, CD10 (subset), and C-MYC (90%), and are negative for CD30, CD5, and CD23. The Ki67 proliferative fraction is ~60%. The small admixed lymphocytes are small mature CD3+ CD5+ T-cells.
Cytogenetics: FISH assays demonstrated MYC rearrangement in 58% of cells. The assays did NOT show BCL6 rearrangement or BCL2-IGH fusion.
nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[29/50],(BCL6x2)[50],(IGH@,BCL2)x3[21/50]
Molecular studies: None
Proposed diagnosis: Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT)
Interesting feature(s) of submitted case: The morphology and non-germinal center immunophenotype, in the current clinical context (restricted presentation of skin lesions on the lower legs of an elderly woman), is highly characteristic of primary cutaneous diffuse large B-cell lymphoma, leg-type (PCLBCL-LT). The patient's history of treated CLL introduces an interesting complication and raises the possibility of cutaneous involvement by Richter's transformation of the patient's previously diagnosed CLL.

After initial presentation, the patient developed more nodules on the right leg, and was treated with rituximab/R-CHOP. The lesions resolved but re-appeared one month later and were re-treated with brachytherapy. A few months afterwards, she developed a new 1cm pink nodule on her left lateral distal leg (contralateral side), again with no evidence of lymphadenopathy or systemic disease. To date (three years from diagnosis), the patient has undergone radiotherapy to her left leg several times and was treated with Rituxan-Revlimid with resolution of her lesions. However, she subsequently developed new skin lesions, still limited to her legs. The restricted presentation of skin lesions on the lower legs without evidence of systemic involvement (no lymphadenopathy or circulating disease) for three years strongly argues against Richter's transformation, and is consistent with PCLBCL-LT. We plan to perform targeted sequencing on this case to assess for the presence of mutations recurrently found in PCLBCL-LT.

EAHP18-LYWS-527

Unusual CD30+ cutaneous lymphoid proliferation in HIV ?ALCL, florid LyP or something else?

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Case description: A 58 year old HIV positive (diagnosed in 2010) male, presented in January 2017 with extensive widespread nodules (5mm to 40mm) on his face, trunk and limbs. Some became ulcerated or necrotic, while others resolved spontaneously leaving post-inflammatory hyperpigmentation. Past history of classical HOdgkin lymphoma (CD30+, CD15+, EBV+) in 2016 in axillary biopsy. Limited stage, treated with ABVD.
The clincal impression initially was Lyphomatoid papulosis or involvement by known lymphoma. He had axillary and inguinal small volume lymphadenopathy but was systemically well, with no B symptoms. Patient had skin biopsies (Jan and Feb 2014) from the lesions (ref 3561 and 9191) and a lymph node biopsy (inguinal node 17S10189) - all have been submitted.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: NO
Details of microscopic findings: Punch biopsy of non-ulcerated skin with a dense dermal (and subcutaneous) lymphoid infiltrate of pleomorphic medium to large lymphoid cells, some with anaplastic morphology, frequent mitoses and apoptosis. There are no classical HOdgkin/Reed-Sternberg cells. There is no epidermotropism. No admixed inflammatory cells are noted.
CONCLUSION: The features are those of a CD30+ lymphoproliferative disorder. The main differential diagnosis is between lymphomatoid papulosis and anaplastic large cell lymphoma. The immunoprofile favours the former. However, clinical correlation is essential in establishing the final diagnosis. NO evidence of Hodgkin lymphoma.
Immunophenotype: Immunostains highlight diffuse expression of CD30 with co-expression of CD2, CD3, CD5, CD4 and MUM1/IRF4 but no expression of CD15, CD8, TIA-1, EBV (EBER), ALK1, EMA, CD20, CD10, CD7, CD56 or MYC protein. There is weak staining for CD25. The proliferation fraction is nearly 100%.
Cytogenetics: Not done
Molecular studies: None
Proposed diagnosis: CD30+ cutaneous lymphoproliferative lesion(s). The differential diagnosis includes Anaplastic large cell lymphoma, Alk negative (preferred at the time and treated as such) and Lymphomatoid papulosis.
Interesting feature(s) of submitted case: There was preceding classical Hodgkin's lymphoma (follow up PET in Nov 2016) with the skin lesions devloping 2-3 months later (january 2017). These were widespread and though the clinical presentation favoured anaplastic large cell lymphoma, however, there were many atypical features for ALCL - history of spontaneous resolution of some lesions, the immunophenotype - continued absence of cytotoxic granule expression in the neoplastic cells, A relatively superficial infiltrate and despite axillary and groin lymph node involvement by disease - biopsies in March 2017- arguably, these involved only the lymph nodes draining the skin lesions and could this represent 'secondary' (dermatopathic type) lymph node involvement rather than primary lymph node disease and were we over interpreting this? I still am in two minds whether this could be florid LyP in the presence of immunosuppression? Could not find any data to support this. So hoping to hear thoughts from the panel. There was excellent response to anti CD30 (Brentuximab) treatment.

EAHP18-LYWS-529

A subcutaneous indolent T-cell lymphoma with a T-zone pattern

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Case description: A 47-year-old man previously operated in 2011 for a thymic carcinoid. In 2016 he consults a dermatologist for multiple subcutaneous nodules located at the right- and left elbow, on the right upper arm and behind the left ear. No other signs or symptoms of disease.
In 2017 a subcutaneous nodule on the right arm is excised (T15035-17)
Biopsy fixation details: 1. A punch biopsy from the right elbow (B6342-16) was routinely fixed in formalin and paraffin embedded.
2. In 2017 a subcutaneous nodule on the right arm is excised (T15035-17). The unfixed tissue measured 40x25x15 mm in size. The tissue was prepared for histopathology, flow cytometry and molecular analysis
Frozen tissue available: Yes
Details of microscopic findings: 1. A skin biopsy with an extensive lymphocyte predominated infiltrate involving mostly the deeper parts of the biopsy. No epidermotropism is seen or infiltrate of adenexal structures. CD4+, CD7dim/reduced T-cells dominate with more scarce B-cells. Ki67-staining shows low proliferation.
2. Histologically the nodule was dominated by a lymphoid infiltrate where B-cell follicles with follicle centres are separated by expanded T-zones. The cells in the T-zones were mainly small to intermediate in size with a clear cytoplasm. There was an increase in vessels and some eosinophils.
Immunophenotype: 1. **Skin biopsy**: **IHC profile:** CD2+, CD3+, CD4+, CD5+, CD8- CD7-/reduced, Ki67 low.
2. **Subcutaneous nodule: Flow cytometry:** A T-cell population (31%) with an abberant CD3-negative phenotype was seen (CD2+, CD3-, CD4+, CD5+, CD7-, CD8-, CD45RO+)**. IHC profile:** CD2+, CD3+, CD4+, CD5+, CD8- CD7-/reduced, Ki67 low. ICOS is positive but no other Tfh-markers (CD10, bcl6, PD1, CXCL13)
Cytogenetics: Not done
Molecular studies: 2. PCR analysis of the nodule showed clonal bands for TCRG and TCRB with Biomed-2 primers.
Proposed diagnosis: 1. **Skin biopsy:** A primary cutaneous small/medium-sized CD4-positive T-cell lymphoproliferative disorder.
2. **Subcutaneous nodule:** Peripheral T-cell lymphoma NOS, with a T-zone pattern in a subcutaneous lesion.
Interesting feature(s) of submitted case: Initial skin lesion compatibel with a primary cutaneous small/medium-sized CD4-positive T-cell lymphoproliferative disorder. At that time however multiple lesions were already present but the patients had no other signs or symptoms of disease. A year later a subcutaneous nodule showed an indolent T-cell lymphoma with a T-zone pattern essentially with the same phenotype and low proliferative activity.
Should this case still be considered a lymphoproliferative disorder or does it qualify for a lymphoma diagnosis?

EAHP18-LYWS-541

Cutaneous PTCL, NOS or lymphoproliferative disorder, with a TFH phenotype

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Case description: A 79 year-old man was admitted because he had sub-mental and pre-tragian cervical adenopathies. He had received no new medications (sitagliptine and glimepiride since 10 years; simvastatine since 15 years). Blood cell count was normal but blood l flow cytometry revealed a slight abnormal T-cell population with a CD4+, CD7-, CD26- and KIR3DL2- phenotype. PET-scan highlighted the adenopathies (SUV: 4.5). Bone marrow biopsy was normal. A nodal biopsy was performed showing a minimal infiltration of the inter-follicular areas by an atypical T-cell population showing an abnormal TFH profiles (TCRbeta+, CD2+, CD3+, CD4+, CD7+, CD30-, CD10+/-, PD1+, $ICOS^{Dim}$, BCL6-). A dominant T-cell clone was evidenced in both the node and blood.
The adenopathies spontaneously regressed within one year but he rapidly developed a severe and diffuse pruritus together with a skin eruption made of small erythematous papules. The skin eruption was resistant to topical steroids treatment. Two skin biopsies were thus perfomed, 6 months and approximately one year after the nodal biopsy, respectively. At the time of skin biopsies, there were no other localization, with normal clinical examination and PET-Scan. The skin eruption is still present despite a treatment with methotrextate at 15, then 20 mg per week.
Biopsy fixation details: Formalin
Frozen tissue available: Yes
Details of microscopic findings: The same atypical lymphocytic infiltrate was evidenced in the two skin biopsies. In the first, the infiltrate was mostly made of “Pautrier’s abcesses” within the follicular epithelium. Only few perivascular atypical cells were seen around dermal capillaries; In the second biopsy, the pilotropism was still present but the infiltrate was mostly seen in the superficial dermis with an overlying scratching ulceration of the epidermis. The atypical lymphocytes showed medium sized hyperchromatic nuclei with irregular shapes and sometimes Sezariform morphology.
Immunophenotype: The atypical lymphocytes expressed T-cell markers with no pan T-cell antigen loss (CD2+, CD3+, CD5+ and CD7+) and were mostly TCRbeta+ and CD4+. They weakly (first skin biopsy) or strongly (second biopsy) expressed CD30 and the TFH markers. The stainings for CD25 and FoxP3 were weakly positive in few lymphocytes. EBER in situ hybridization was negative.
Cytogenetics: None
Molecular studies: TCR rearrangement studies (gamma chain PCR) showed a monoclonal aspect in the skin and blood. A targeted deep sequencing study is ongoing.
Proposed diagnosis: Cutaneous PTCL,NOS or lymphoproliferative disorder, with a TFH phenotype
Interesting feature(s) of submitted case: The classification of this lymphoma is difficult. The clinical and pathological features are not consistent with folliculotropic mycosis fungoides and Sézary syndrome or the primary cutaneous CD4+ small medium T-cell lymphoproliferative disorders. The spectrum of the clinical and pathological presentation of this latter entity is now better described. Although readily atypical cells were present within the infiltrates, the patient has a favorable outcome despite resistance to first and second line treatments with topical steroids and methotrexate. This case illustrate the possible occurrence of cutaneous PTCL,NOS with TFH features, which can be regarded as the cutaneous counterpart of the nodal PTCL,NOS or follicular PTCL.

EAHP18-LYWS-543

Panniculitis or more...tricky T-cell presentation

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Case description: 31 year old afrocarribean female with SLE and sickle cell anaemia, on Hydroxycarbamide and hydroxychloroquine. Had ongoing fevers since late March 2015, admitted in April with sickle sequestration crisis. She then developed (over a week) tender, erythematous, firm, subcutaneous plaques on the arms, abdomen, chest. Similar episode 1 month ago which resolved. ?nodular vasculitis/erythema induratum. ?other panniculitis/?atypical mycobacterial infection. Had skin biopsies in 2015 and early 2016.

Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: These biopsies show largely unremarkable epidermis (except minimal exocytosis of lymphocytes and plasma cells). The dermis show varying degrees of perivascular lymphoplasmacytic inflammation and areas of increased dermal mucin (2016 biopsies). The main abnormality is in the subcutis which shows a moderately prominent, predominantly lobular lymphoplasmacytic infiltrate with histiocytes that spills over into the septa and adjacent deep reticular dermis. There is patchy necrosis of the fat lobules. The infiltrate iincludes few atypical lymphoid cells that surround the adipocytes (“rimming”) with interstitial apoptotic nuclear debris which is phagocytosed by adjacent histiocytes (so called bean bag cells).

Immunophenotype: Predominantly T-cell infiltrate expressing CD2, CD3, CD5 (weak) and CD7 (weak) with 'cytotoxic' phenotype - CD8+, TIA1+ in cells rimming adipocytes. CD56 and CD4 (few) are largely negative. Few CD123+ small aggregates of PDCs and few small B cell (CD20+, CD79a+) clusters noted. Rare CD30+ve cells at the periphery of the lobules. The proliferation fraction as measured by expression of Ki67 is high in "hot spots" (60-70%). EBV in-situ probe for EBER is negative.

Cytogenetics: NA
Molecular studies: IgH gene rearrangement: DNA is of insufficient quantity or quality for analysis.
T-Cell receptor B: Positive for the detection of clonal T cell receptor beta chain or gamma chain gene rearrangement(s) consistent with the presence of a clonal cell population.
Proposed diagnosis: Subcutaneous panniculitis-like T-cell lymphoma on a background of systemic lupus erythematosus and sickel cell disease with overlap between lupus erythematosus
Interesting feature(s) of submitted case: The clinical features (see photos) were suggestive of panniculitis but the histological features show an overlap between the findings associated with lupus erythematosus and subcutaneous panniculitis like T-cell lymphoma. The patient had biopsies in 2015 and 2016 which show similar features and only had treatment targeted at LE/Sickel cells and did not receive chemotherapy. She improved and is being followed up clinically. She remains well (except for her ongoing LE and Sickle cell related clinical issues). Overlap with lupus is a diagnostic difficulty and requires careful evaluation, sometimes with repeat biopsies and resolves in the absence of conventional chemotherapy for subcutaneous panniculitis like T cell lymphoma - otherwise treated aggressively.

EAHP18-LYWS-547

"Primary cutaneous marginal zone lymphoma showing light-chain switch "

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Case description: A 68-year-old man presented with an asymptomatic subcutaneous nodule on his right thigh of several weeks duration. The patient denied having suffered a previous Injury, local or systemic infections or injections at this site. Physical examination showed a non-tender, erythematous subcutaneous nodule measuring 1.3 cm in greatest dimension. No further cutaneous or subcutaneous tumors or enlarged lymph nodes were detected at that time. 14 months later a well circumscribed plaque was detected on the patient's back.
Biopsy fixation details: 10% buffered formaline.
Frozen tissue available: Not available
Details of microscopic findings: Histopathologic examination of the thigh nodule showed an unremarkable epidermis with an underlying Grenz zone and a dense periadnexal dermal infiltrate, focally reaching the subcutis. It consisted mostly of small lymphocytes with round, hyperchromatic nuclei, as well as centrocyte-like cells, lymphoplasmacytoid cells, and plasma cells, admixed with small numbers of centroblast- or immunoblast-like cells and many reactive small lymphoid cells . Biopsy of the back plaque revealed a similar, perivascular and periadnexal infiltrate of small, mature lymphocytes admixed with plasma cells.
Immunophenotype: Immunohistochemical studies of the tumor on the right thigh demonstrated a predominance of CD20-positive B-cells (with some intermingled CD3-positive T-cells) that co-expressed BCL2 but stained negative for CD10, BCL6 and Cyclin D1. Plasmacytic differentiation was mainly observed in sheets and clusters towards the margins of the neoplastic lymphoid infiltrates with expression of IgG and overwhelming expression of IgG4 (90 %). There was evidence of kappa light chain restriction with only few reactive plasma cells positive for lambda light chain. Of note, immunohistochemical staining for IgA, IgM or IgD was negative in the neoplastic infiltrate. There were scattered PD-1 positive T-cells.
The plaque on the back demonstrated abundant CD20-positive B-cells with an admixture of CD3-positive T-cells. However, in contrast to the initial lesion, the plasma cells now displayed a frank predominance of immunoglobulin lambda light chain expression with a kappa : lambda ratio of greater than 1 : 10. Staining for IgG was positive also in the neoplastic plasma cells. Only residual germinal centers and colonized follicular germinal centres were highlighted by BCL6 and CD23, respectively. Given this discrepancy, an in situ hybridization study for immunoglobulin light chain expression was repeated on both specimens, and the findings were confirmed.
A third sample corresponding to a local relapse of the second lesion displayed lambda light-chain restriction.
Cytogenetics: Not have
Molecular studies: Both PCMZL samples were studied by IgVH PCR and the FR1 and FR2 results show similar clonal peaks, with small differences, suggesting that both samples contain the same IgVH clone. A clonal TCR rearrangement was identified only in the second sample. The analysis of the third sample only displayed a polyclonal IgVH rearrangement.
Proposed diagnosis: Primary cutaneous marginal zone B-cell lymphoma
Interesting feature(s) of submitted case: We report a rare case of primary cutaneous marginal zone lymphoma showing light-chain switch from kappa to lambda. Similarity of the IgVH rearrangements support the identity of both B-cell clones. This is an unusual finding, not previously recognized in primary cutaneous marginal B-cell lymphoma, and described to be associated with tumoral progression in follicular lymphoma.

EAHP18-LYWS-559

A very uncommon presentation of a primary cutaneous diffuse large B-cell lymphoma, leg type

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Case description: This 67-year old woman without significant clinical history presented with nasal obstruction (10/2007). A diagnosis of diffuse large B-cell lymphoma was made following an excisional biopsy of a voluminous polyp of the right nasal cavity. Physical examination revealed neither B symptoms nor lymphadenopathy, but a small bluish-red skin lesion on the back of the left leg. A small biopsy of this lesion was performed and showed a localization of a diffuse large B-cell lymphoma. The laboratory results were normal, except the LDH level (450UI/l). There was no bone marrow or cerebrospinal fluid involvement. PET/CT showed no other sites of disease. The patient was treated with R-CHOP + intrathecal Methotrexate (8 cycles). A complete response was obtained but 6 months later (11/2008) a local recurrence was observed on the left leg. A high-dose chemotherapy (R-ICE = iphosphamide-etoposide-carboplatine) with autologous stem cell transplantation was performed. One year and a half later (05/2010) a local recurrence on the back of the left leg was treated by surgery. Four months later (09/2010) the patient presented two biopsy-proven recurrences on the left arm and forearm which were treated by radiotherapy. One year later (09/2011) the patient underwent radiotherapy on the left forearm for a local recurrence. Three months later (12/2011) a recurrence on the left nasal cavity was treated with complete excision by surgery. There were multiple relapses since then on the left nasal cavity, the left arm and the left leg treated by surgery or radiotherapy.
Biopsy fixation details: Formalin
Frozen tissue available: Yes
Details of microscopic findings: Histologic sections of the polyp of the right nasal cavity show a diffuse and monotonous infiltrate composed of centroblasts and immunoblasts with vesicular chromatin and proeminent nucleoli. The mitotic activity is high.
Histologic sections of the skin biopsy show a non epidermotropic dermal infiltrate composed of confluent sheets of centroblasts and immunoblasts.
Immunophenotype: The lymphoma cells are positive for CD20, bcl2, MUM1. CD10 and bcl6 staining are negative. MYC staining is positive. The proliferation index is very high (> 90%). There is no follicular dendritic cells. Small reactive T cells are positive with CD5.
Cytogenetics: No
Molecular studies: No
Proposed diagnosis: Primary cutaneous diffuse large B-cell lymphoma, leg type
Interesting feature(s) of submitted case: First extra-cutaneous presentation.
Multiple skin lesions.
Slowly evolution with multiple local relapses

EAHP18-LYWS-567

Lymphomatoid papulosis with marked stromal eosinophilia presented as a large ulcerated shin lesion

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Case description: A 3-year-old female presented with rapidly enlarging left shin ulcerated lesion, measuring 5x3x2 cm. She was otherwise asymptomatic.
Biopsy fixation details: Punch biopsy was performed and fixed in formalin.
Frozen tissue available: None
Details of microscopic findings: Microscopically the biopsy revealed a superficial and deep dermal infiltrate composed of scattered large atypical cells with pale cytoplasm, oval to convoluted nuclei, vesicular chromatin, and prominent eosinophilic nucleoli, within a background of numerous eosinophils, abundant histiocytes, and focal necrosis. Mitotic figures were easily identified. The large atypical cells were enriched in focal areas, forming small aggregates, but less numerous and showed scattered distribution in other areas. The infiltrate also extended deep into the subcutaneous fat, but epidermis was not involved.
Immunophenotype: The large atypical cells were positive for CD3, CD4 and CD30, negative for CD8 and ALK, and demonstrate high proliferative rate by Ki-67 IHC stain. CD20 and PAX-5 highlighted rare benign B cells. CD68, CD163, and lysozyme highlighted numerous background histiocytes. S100 showed melanocytes in the epidermis and occasional interdigitating dendritic cells in the dermis. GMS, PAS, and Gram stains revealed no microorganisms.
Cytogenetics: None
Molecular studies: PCR for T-cell receptor gamma-chain gene rearrangement was performed and showed a prominent clonal peak.
Proposed diagnosis: Primary cutaneous CD30+ T-cell lymphoproliferative disorder, consistent with lymphomatoid papulosis.
Interesting feature(s) of submitted case: Primary cutaneous CD30+ T-cell lymphoproliferative disorders comprise a spectrum of skin lesions ranging from lymphomatoid papulosis to primary cutaneous anaplastic large cell lymphoma. Some cases demonstrate overlapping features and a definite diagnosis of one versus another may not be possible.
The unusual features of our case include large size (5cm in greatest dimension) triggering high clinical suspicion for lymphoma, and marked stromal eosinophilia resembling another mucosal lesion described in the oral cavity- traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), however quick and complete response to steroid and antibiotics, suggesting a non-malignant nature.
Recognition of these unusual features will promote accurate diagnosis and correct management of challenging LyP cases.

LYMPHOMA WORKSHOP SESSION 2

Lymphoproliferative disorders in immune privileged sites

Chairs: R. King, J. Ferry

EAHP18-LYWS-100

Clonal Evolution in a case of Central Nervous System Large B cell lymphoma with testicular relapse

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Case description: A 60 year old man presented with dysphasia and hearing loss of 3 months of duration. Cerebral MRN disclosed an expansile lesion in the left temporal lobe. Surgical biopsy was done. The patient was treated with PCNSL protocol including MTX and high dose intensification, previous to autologous stem cell transplantation, that was performed without complications. 18 months after the initial diagnosis a suspicious mass in the left testis was found by ultrasound scan. Left orchiectomy was done.
Biopsy fixation details: Both samples were Formalin fixed and paraffin embedded.
Frozen tissue available: NO
Details of microscopic findings: The tumors showed a diffuse large cell population with characteristic perivascular cuffing in the central nervous sytem lesion.
Immunophenotype: Both lesions showed identical phenotype. CD20 was positive and IHC disclosed a non-GCB profile with coexpression of MYC and BCL2. EBV-EBER and PD-L1 (clone 22C3) were negative.
Cytogenetics: FISH for MYC, BCL2 and BCL6 translocations showed a normal pattern, ruling out a DH High grade B cell lymphoma in both samples.
Molecular studies: Clonality testing demonstrated clonal relationship with identical FR3 clonal rearrangements (117 bp). Targeted exonic NGS of both samples and germline PB granulocytes showed a highly heterogeneous mutational profile in the CNS sample, with few dominant and potentially driver mutations (MYD88L265P, EZH2, FAT2, ATM, SMARCA4) and multiple co-ocurring subclonal mutations in a variety of genes, including tumor suppressor genes (PRDM1, TP53) and genes involved in the NOTCH pathway (NOTCH1, NOTCH2 and SGK1). Only MYD88L265P and a novel CD79BY196S mutation appeared in the second sample from the patient.
Proposed diagnosis: Central Nervous system, ABC'type Large B cell lymphoma with systemic relapse in immunoprivileged site (testis)
Interesting feature(s) of submitted case: Systemic relapse of PCNSL is uncommon (15%), and frequently involves extranodal sites, including the testis.
Targeted NGS annalysis of the primary and relapsed sample reveal significant genetic dynamics despite stable phenotypic and cytogenetic features. A clonal selection ocurred with a reduction in the number of mutations found in the relapse and emergence of CD79BY196S mutation. The presence of MYD88L265P mutation in both samples at similar VAF suggest its role as a founder mutation.
Based on recently published clinical data, the presence of the combination of MYD88L265P and CD79B ITAM mutations in the relapse sample might have therapeutic implications

EAHP18-LYWS-376

Diffuse large B-cell lymphoma of the testis and central nervous system

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Case description: The patient is a 61-year-old male with a history of diffuse large B-cell lymphoma (DLBCL) of the brain treated with multiple chemotherapeutic drugs and whole-brain irradiation. Five months after initial diagnosis, he noted a right testicular mass and underwent orchiectomy. Right ocular globe involvement was subsequently detected and treated with radiation. He then showed central nervous system (CNS) disease progression and chemotherapy was restarted. Despite this, his disease progressed and therapy was discontinued. He expired nearly one year after initial diagnosis. He never had evidence of disease outside the CNS or testis.
Biopsy fixation details: No material from the CNS DLBCL was available, therefore, the right orchiectomy (formalin-fixed) is submitted.
Frozen tissue available: No
Details of microscopic findings: The CNS DLBCL was composed of large lymphoid cells positive for CD20 by immunohistochemistry (IHC). The testicular mass showed a diffuse infiltrate of medium to large lymphoid cells with scant to moderate amphophilic cytoplasm, irregular nuclear contours, vesicular chromatin, and one or more nucleoli. They showed partial destruction of the testicular architecture and infiltration of many residual seminiferous tubules.
Immunophenotype: By IHC, the tumor cells expressed CD20, CD10, MUM1 and BCL2 (>50%). They showed loss of normal expression of MHC class I, beta2-microglobulin (B2M), MHC class II and CIITA. They lacked BCL6, CMYC, PD-L1, PD-L2 and PD-1 expression. Ki-67 proliferation index was up to ~60%.
Cytogenetics: SNP array showed multiple copy number losses and gains, including homozygous copy number loss of chromosome 6p21.33 (contains HLA-B/-C genes) and 9p21.3 (contains CDKN2A/B genes).
Molecular studies: We performed comprehensive genomic sequencing using a hybridization capture-based next-generation sequencing assay that evaluates 585 genes. Barcoded libraries from tumor DNA were captured, sequenced, and subjected to a custom analysis pipeline to identify somatic mutations. The following mutations were detected:

MYD88 p.L265P
BMPR1A p.R486W
ETV6 X11_splice
TBL1XR1 p.Y395C
ATRX p.S566Y
CCND2 p.P53L
FANCA p.S890N
KIT p.N268I
PIM1 p.E32Vfs*45
TP53 p.L350R
LATS2 p.Q413L
MEF2B p.F21V
BTG1 p.G30E
BTG1 p.V19M
TBL1XR1 p.N129Kfs*14
ASXL3 p.A140V
MYO18A p.Q1433P

Proposed diagnosis: Diffuse large B-cell lymphoma of the testis
Interesting feature(s) of submitted case: Primary DLBCLs of CNS and testis have characteristic genetic alterations. Compared to systemic DLBCL, they more commonly harbor mutations of genes involved in the NF-kappaB, B-cell receptor and toll-like receptor signaling pathways, including MYD88 (present in our case) and CD79B, which likely cause enhanced cell proliferation and decreased apoptosis. They more frequently show chromosome 9p21.3 (CDKN2A/B locus) copy number loss, which is often biallelic (present in our case) and may

lead to altered cell cycle regulation. Alterations of genes involved in immune escape are frequent, including loss of chromosomes 6p21.33 (HLA locus) (present in our case) and 15q21.1 (B2M locus) and HLA-A and B2M gene mutations. Chromosome 9p24.1 (PD-L1/PD-L2 locus) copy number gain and PD-L1/PD-L2 translocations are also more common. Many tumors show loss of MHC class I/II and B2M expression (present in our case) and over-expression of PD-L1/PD-L2 by IHC. Such genetic alterations have potential treatment implications, including use of targeted therapies, particularly as these tumors respond poorly to conventional therapy. They also point to common oncogenic mechanisms in CNS/testis DLBCL, which primary cutaneous DLBCL, leg type may also share.

EAHP18-LYWS-550

A rare combination of diseases in the brain, how to treat?

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Case description: In September 2017 a 57-yearold female patient presented with continuous headaches, muscle weakness and trembling of the left hand, balance disorders and memory loss. Also paresis of the facial nerve was present. Lab results showed leucopenia and anaemia.
In 2004 she had been diagnosed with Waldenstrom macroglobulinaemie (IgM kappa, MYC88 L265P gene mutation present) and treated with erythropoeietin and iron-substitution. Because of severe neutropenia she received chemotherapy in 2012 (rituximab and chlorambucil) and again in 2016 for anaemia and bone marrow localization of the disease.
In additional testing of the cerebrospinal fluid an increased number of leucocytes (of which 27% B-cells) was found, positive for JC- virus (PCR). An MRI brain showed irregular tumors in both frontal lobes and lepto-meningeal enhancement. An MRI whole spine showed an epidural mass, infiltrating retroperitoneal fat tissue. A brain biopsy was performed and both progressive multifocal leuco-encephalopathy (PML) as a lymfo-plasmocellular lymphoma (Bing-Neel syndrome, lambda) was diagnosed. She was treated with medication (steroids, mefloquine and mirtazapine) and radiotherapy (20 x 2 Gray), after which she clinically improved. Partial remission was achieved and lasting (last follow-up January 2018).
Biopsy fixation details: 4% buffered formalin
Frozen tissue available: no
Details of microscopic findings: Brain biopsy: Brain tissue with influx of lymphocytes and plasmacells. Furthermore reactive, atypical astrocytes were present, as well as foamy histiocytes and oligodendrocytes with enlarged hyperchromotic nuclei.
Immunophenotype: mixed cell population CD20 + lymphocytes, CD3 + lymphocytes and plasmacells (CD138, lambda). BK-staining (proxy for JC-virus) was positive
Cytogenetics: no
Molecular studies: Brain material of insufficient quality for molecular testing
Proposed diagnosis: Both progressive multifocal leuco-encephalopathy (PML) and localization of lymfo-plasmocellular lymphoma (Bing-Neel Syndrome)
Interesting feature(s) of submitted case: This case represents a combination of two rare diseases in the brain. Bing-Neel syndrome is a rare neurologic complication of Waldenström macroglobulinaemie (1% of patients). Progressive multifocal leuko-encephalopathy (PML) is a rare disease, characterized by progressive damage of the white brainmatter caused by the JC-virus in immunocompromised patients (eg use of rituximab). Both diseases have a high mortality rate and have opposite treatment therapies, resulting in a clinical dilemma. Additional H&E stained slides are not available for the workshop, due to limited material. The case can be extensively documented with photographic material.

EAHP18-LYWS-156

Seroma-confined breast implant-associated anaplastic large cell lymphoma

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Case description: A 58 year old woman presented in January 2017 with a 4 week history of a swollen left breast following a fall. Bilateral breast silicone implants were in situ since 2006 following mastectomies and axillary node sampling for ductal breast carcinoma. She had received adjuvant radiotherapy, chemotherapy and tamoxifen. In 2007 she required revision reconstructive surgery and had the first set of silicone implants removed with bilateral capsulectomies, dog ear skin excisions from the lateral ends of the mastectomy scars, and replacement of the silicone implants.
In January 2017 the patient had the left seroma aspirated and the left capsule was biopsied. This was followed by complete bilateral capsulectomies and submission of the left seroma contents in February 2017.
Biopsy fixation details: PAP and Giemsa stained smears and cytospins were prepared from the seroma fluid. The natural clot and prepared clot from the seroma and the capsular tissue were fixed in neutral buffered formalin.
Frozen tissue available: No
Details of microscopic findings: The seroma fluid was very cellular and contained abundant discohesive large malignant cells with pleomorphic nuclei and plentiful pale cytoplasm . Some cells had eccentrically placed nuclei with prominent nucleoli. Mitoses were visible. Some mixed inflammatory cells were present in the background.
The capsule biopsy and capsulectomy specimens showed hyalinised fibrous tissue with focal foreign body inflammatory reaction to leaked silicone. There was no histological evidence of tissue involvement by tumour, despite extensive sampling.
Immunophenotype: The malignant cells were positive for CD45, CD3, CD2, CD5, CD8, Granzyme B, CD43, bcl2 and CD30 (strong and diffuse). EMA was positive in a minority of malignant cells. mib1 immunostaining showed a proliferation index of approximately 85%.
Alk1, CD20, CD68, pan-cytokeratin AE1/3, Ecadherin, ER and PR were all negative in the malignant cells.
The capsulectomy specimens were CD30 negative.
Cytogenetics: Not performed.
Molecular studies: PCR was performed on the seroma cell block, and showed clonal rearrangements of both TCRγ and TCRß genes.
Proposed diagnosis: Breast implant associated anaplastic large cell lymphoma
Interesting feature(s) of submitted case: The diagnosis of this case hinged on the submission of the seroma fluid, as the lymphoma did not involve the implant capsule. Sending implant seroma fluid to Cytology should be standard procedure to avoid missing the diagnosis.

EAHP18-LYWS-572

Gastric silicon band associated ALK-negative anaplastic large cell lymphoma

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Case description: A 62 year old obese female with a known history of chronic lymphocytic leukemia had a gastric silicon-based lap band placed along with a control port and tubing 6 years earlier. Her past medical history included type 2 diabetes mellitus, hypertension, supraventricular tachycardia, optic neuritis, fibromyalgia and depression. Her CLL was diagnosed 10 years earlier when it presented with Rai stage 0 disease and a moderately complex karyotype characterized by structural abnormalities including an 11q deletion (ATM). She received chemotherapy with Fludarabine, cyclophosphamide and rituximab and attained a complete remission for 6 years. After relapse, she received bendamustine and rituximab and attained a partial remission. About 2 years after her last treatment for CLL, a mass was noted in the epigastric area in proximity to the lap band reservoir. An abdominal ultrasound demonstrated a fluid collection measuring 5.6 x 3.0 x 5.3 cm. A subsequent CT scan demonstrated a lobulated, rim-enhancing fluid collection in the anterior abdominal wall, distinct from the subcutaneous reservoir. A percuatenous needle drained no significant fluid. A needle biopsy was followed by an excision of the mass and removal of the lap band.
Biopsy fixation details: The biopsy was fixed in neutral buffered formalin fixative.
Frozen tissue available: Frozen tissue was obtained.
Details of microscopic findings: Large cells with C-shaped or reniform nuclei are infiltating in the soft tissue in the mass that was located along the tubing in the abdominal wall. There was no extension into the skin or into visceral organs. In addition, there were small B-cells present of the known chronic lymphocytic leukemia that were CD20, CD5, and CD23 positive.
Immunophenotype: Flow cytometry showed no aberrant T-cell phenotype with a CD4:CD8 ratio of 1:1. Immunohistochemical slides showed the large cells were positive for CD3, CD30, CD4, CD5, CD43, TIA-1, Granzyme B: and negative for CD20, CD2, CD7, CD8, CD23, and ALK.
Cytogenetics: 50 XX +2, +8, +22, +mar [3]/46XX [17]
Molecular studies: T-cell receptor gamma PCR pending.
Proposed diagnosis: ALK-neg Anaplastic Large Cell Lymphoma, Gastric band implant associated
Interesting feature(s) of submitted case: Cases of anaplastic large cell lymphoma associated with silicon based breast implants are well known to occur in the capsule surrounding the implant. This is the first reported case of a gastic band associated anaplastic large cell lymphoma. This case may have a similar antigenic stimulation basis for an implant associated lymphoma as in breast implants.

EAHP18-LYWS-353

Diffuse Large B-cell Lymphoma, Non-Germinal Center-Like, Double-Expresser Type, Arising in a Sporadic Atrial Myxoma, Showing a Central Nervous System Diffuse Large B-Cell Lymphoma-Like Mutational Pattern (Pathogenic Mutations in PIM1 and ETV6 Genes)

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Case description: A 50-year-old female presented in 1998 with fatigue, dyspnea and palpitations. EKG showed atrial fibrillation. Transthoracic echocardiography showed a 6 cm left atrial mass attached to the atrial wall and protruding through the mitral valve into the left ventricle causing mitral regurgitation. Chest x-ray showed cardiomegaly. Physical examination did not show palpable lymphadenopathy. Left atrial mass and a portion of the atrial wall were resected. Grossly it was a mottled, yellow-tan, focally hemorrhagic, fungating, 6.2 x4.2 x3.2 cm, friable, mass with attached 2.7 x 2.2 x 0.4 cm portion of atrial wall. Its cut surface was yellow-tan-red and myxomatous. A diagnosis of DLBCL involving an atrial myxoma was made. CT scan of chest, abdomen and pelvis showed no abnormalities. Bone marrow was not involved by lymphoma. There was no evidence for Carney's Complex. She did not receive chemotherapy or any other treatment for DLBCL. During last 20 years of follow-up, palpitations have persisted, EKGs/echocardiography have shown only mild abnormalities, no lymphadenopathy/organomegaly has been noted on physical exam and on CT scans.
Biopsy fixation details: 10% Neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: H and E sections show a papillary mass with arrays of large atypical lymphoid cells mainly on the surface. The atypical lymphoid cells are large with high N:C ratio, prominent nucleoli and many mitotic figures. Surface endothelium of the mass is continuous with the endocardium. Atrial wall is uninvaded by lymphoid cells. Under the lymphoid cell layer, the body of the mass is composed mostly of fibrin and blood vessels with perivascular and intervascular myxoid change.
Immunophenotype: Endotheliium and endocardium are CD34+. Positive stains in lymphoid cells: CD20, CD79a, BCL2, BCL6, MUM1, p53, MYC, and Ki67 (~99%); Negative stains in lymphoid cells: CD3, CD5, CD10, CD30, BCL1, EMA, EBV-LMP1, EBER (by ISH) and PD-L1.
Cytogenetics: Not done
Molecular studies: **FISH for BCL6, MYC and MYC/IGH:** Rearrangement and/or partial deletion involving BCL6; 3 or 4 copies of the MYC gene; Gain of all or part of chromosome 8 (gain of MYC) and gain of all or part of chromosome 14 (probably rearrangement involving IGH and a gene other than MYC, which could be BCL2, but those probes didn't work or it could also be BCL6 [t(3;14)], but we didn't have probes for that.) **Next-Generation Sequencing using 128-gene panel:** Pathogenic mutations are detected in PIM1 gene (C607+1G>T; a SNP; 38% mutant allele frequency) and ETV6 gene (C.367 C>T;qQ123; a missense mutation; 43% mutant allele frequency); Mutations of uncertain significance are detected in BCOR, ETV6, FAT1, HIST1H1E, PIM1, and TBL1XR1 genes.
Proposed diagnosis: DLBCL, non-GC-like, double-expresser type, arising in a sporadic atrial myxoma with extensive fibrin deposition (Fibrin-associated DLBCL) and harboring pathogenic PIM1 and ETV6 gene mutations
Interesting feature(s) of submitted case: (1) DLBCL in a sporadic fibrin-rich atrial myxoma (Fibrin-associated DLBCL) in an immunocompetent patient (2) No association with EBV or HHV8 virus (3) Surgical resection was curative (3) Primary CNS DLBCL-like mutational pattern (PIM1 and ETV6 mutations), suggesting shared underlying pathogenetic mechanisms.[1,2] **(1).** Severson EA, et al. 2017 ASH Meeting Abstract. Blood 2017 130:3996; **(2).** Bruno A, et al. Oncotarget 2014;5(13):5065-5075

EAHP18-LYWS-403

Non-anaplastic breast implant EBV+ lymphoma associated with chronic inflammation

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Case description: Bilateral breast silicone implants were placed in a 61 year-old woman after mastectomy for adenocarcinoma. Thirteen years after implants placement, a PET-scanner showed peri-prothetic right mammary fixation. There was no clinical/biological sign of gravity. Breast needle biopsy revealed abundant fibrin deposits with rare atypical lymphoid cells, expressing CD45 and weak CD30. The patient underwent removal of breast implants and peri-prothetic capsules.
Biopsy fixation details: 4% formalin
Frozen tissue available: no
Details of microscopic findings: The right capsulectomy was infiltrated by a plurinodular tumor composed of sheets of monomorphic large lymphoid cells displaying round nuclei with central nucleoli, and moderate amounts of cytoplasm, with occasional features of plasmablastic differentiation. There was no « hallmark » cell. A starry sky pattern was due to the presence of tingible body macrophages. Mitoses were numerous and some foci of necrosis were noted. The infiltration extended from the luminal ulcerated surface of the capsule to the depth of the resection, where concomitant follicular hyperplasia with numerous germinal centers was present. The adipose and breast tissue were not involved. No lymphoma cell was detected in the bone marrow biopsy and aspirates. The resected axillary lymph node exhibited follicular hyperplasia, without any lymphoma invasion. PET-scan staging did not show other tumor localization.
The left capsulectomy contained abundant fibrin deposits and exhibited polymorphic inflammatory lesions including prominent histiocytic granulomatous reaction and follicular hyperplasia.
Immunophenotype: IHC results showed that lymphoma cells expressed CD45, MUM1, CD10, EMA, Bcl6, CD79a (weak), Kappa light chains, CD4 (equivocal), whereas CD20, PAX5, CD19, CD22, CD138, Lambda light chains were negative. CD30, PD1, and ICOS were focally expressed. Tumor cells were negative for CD2, CD3, CD5, CD7, CD8, CD43, ALK, CD15, CD21, CD56, Granzyme B, Tia1, LMP1, HHV8 and CXCL13. The proliferative index was close to 100%. EBER in situ hybridization was strongly positive.
Cytogenetics: Array CGH analysis showed deletion of 14q32.33, X monosomy, FHIT interstitial homozygous deletion due to loss of 3p14.2 and FOXPD and MDFIC heterozygous deletion due to loss of 7q31.1.
Molecular studies: Clonality analysis showed major B-cell rearrangements, and minor T-cell rearrangements. B-cell monoclonality was confirmed by 2 different experiments performed on different tumor areas, whereas T-cell rearrangements were variable (interpreted as pseudo-clonality). FISH and targeted NGS analysis are in progress.
Proposed diagnosis: Non-anaplastic breast implant EBV+ diffuse large B-cell lymphoma associated with chronic inflammation.
Interesting feature(s) of submitted case: To our knowledge, this is the first reported case of EBV+ breast implant lymphoma. The present observation fits the criteria for diffuse large B-cell lymphoma arising in the setting of chronic inflammation (i.e. mimicking the prototypical pyothorax-associated lymphoma), which has been previously described in a setting of metallic implants or cardiac prosthesis (so-called “fibrin-associated diffuse large B-cell lymphoma”), but not in breast implant patients. The present case opens new insights into the diagnostic pitfalls and pathogenesis of breast implant lymphomas, which might be considered as an inflammation-driven neoplasia.

EAHP18-LYWS-332

HHV8 and EBV-negative effusion-based diffuse large B-cell lymphoma in an 88-year old female.

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Case description: The patient is an 88-year-old female ex-smoker, with a history of colonic adenocarcinoma (2000). For her colon cancer, she had been treated with chemotherapy and subsequently radiation. She experienced cardiac toxicity secondary to chemotherapy.
In May 2017, she presented with a left pleural effusion. A thoracentesis for the effusion led to a diagnosis of diffuse large B-cell lymphoma, effusion-based. Staging did not show any evidence of lymphoma outside the pleural cavity. She was treated with R-CHOP with reduced doses due to prior cardiac toxicity and cardiomyopathy. Follow-up as of January 2018, showed no evidence of lymphoma and stable cardiac function, approximately 7 months after initial diagnosis.

Biopsy fixation details: Neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: A left pleural thoracentesis was performed showing a high content of atypical lymphoid cells. There were sparse mesothelial cells in the background. The atypical lymphoid cells resembled centroblasts/ immunoblasts, with vesicular chromatin, basophilic cytoplasm, easily identified mitotic figures. Cells with apoptotic nuclei were seen.
Immunophenotype: The atypical cells were positive for CD45, CD20, CD79a, MUM1, BCL6, but negative for CD10. (Non-GCB/ or ABC) by the Hans algorithm. BCL2 was focally positive in a subset of tumor cells. MYC showed nuclear staining in approximately 50-60% of tumor cells. CD138, CD30, EBER, and HHV8 were negative. The Ki-67 proliferation index was high (95%).
Cytogenetics: FISH for MYC and BCL2 rearrangements was negative. However, there were extra copies (3-4) of both chromosome 8 and 18, indicative of aneuploidy. FISH for BCL6 rearrangement was negative.
Molecular studies: not done
Proposed diagnosis: Diffuse large B-cell lymphoma, effusion-based, negative for HHV8 and EBV.
Interesting feature(s) of submitted case: This is an example of a “primary effusion lymphoma” negative for EBV and HHV8. The tumor was confined to the pleural cavity. Despite the patient’s advanced age (88 yrs.), and high-grade features of the tumor, she did well with chemotherapy given at reduced doses because of her age and cardiomyopathy due to prior systemic chemotherapy for colon cancer. She achieved a complete remission. Similar effusion-based lymphomas appear to be more common in the elderly. The prognosis appears superior to effusion-based lymphomas positive for HHV8 or EBV.

EAHP18-LYWS-117

Cerebral tumorous amyloidoma within low-grade B-cell lymphoma with plasmacytic differentiation in a patient with rheumatoid arthritis.

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Case description: Presented is a case of a female, born 1946 with a clinical background of rheumatoid arthritis since the age of 54 years treated with daily low-dose solumedrol.
She was admitted for MRI imaging in May 2012 for parestesia in left arm and left part of the face. Imaging revealed an infiltrative intraaxial central lesion with stereotactic surgery following in 10/2012 out of our teaching hospital. Local patholgist preferred a diagnosis of low-grade glioma over a gliosis with a differential diagnosis of pilocytic astrocytoma grade 1 or ganglioglioma. Since 12/12 the patient was only watched and wait.
During a check-up in our Teaching hospital in 9/13 the question of possible discrepancy between MRI and inicial finding was raised and rebiopsy was indicated for 10/13 as well as for continuous symptoms of parestesia in upper and lower left extremity.
Patient is currently lost from follow-up.
Biopsy fixation details: Buffered formalin.
Frozen tissue available: Not available.
Details of microscopic findings: Brain tissue with gliosis and depositions of amorphous material consistent with amyloid with positivity of Congo red and Saturn red stains with yellow-green birefringence. Focal perivascular infiltrates composed of lymphocytes and plasma cells were found.
Immunophenotype: Congo red and Saturn red in amyloid depositions.
CD20 positive B-cells in infiltrates, with predominance of CD138 positivie plasma cells with lambda chain restriction.
CD3 positive admixed T-cells
Immunofluorescence – additionally stained in 2017 for workshop purposes confirmed lambda positivity also in amyloid depositions.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Cerebral tumorous amyloidoma in a setting of low-grade B-cell lymphoma with plasmacytic differentiation in a patient with rheumatoid arthritis.
Interesting feature(s) of submitted case: Low-grade B-cell lymphomas of brain are quite rare. Interesting feature of this case is the autoimmune disease setting, plasmacytic differentiation and production of amyloid with tumorous depositions mimicking glial tumor on MRI.

Comment:
Initial diagnosis of low-grade glioma was determined from small samples of 2-3 mm in diameter according to the original report but the review of slides from another department is currently not available.

EAHP18-LYWS-129

EBV(+) diffuse large B cell lymphoma arising in an adrenal pseudocyst associated with synchronous lymphoplasmacytic lymphoma

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Case description: 58, male presented in 2012 with history of recurrent adrenal cyst which had been deroofed in 2009. He was a known case of lymphoplasmacytic lymphoma since 2005 which was managed by chemotherapy. He underwent a left adrenalectomy in 2012. Postoperative course was without complcations. The patient was followed up till end 2013 when he expired due to non-related causes.
Biopsy fixation details: Formalin fixed paraffin embedded tissue
Frozen tissue available: No
Details of microscopic findings: 2009 cyst deroofing specimen: Lymphoplasmacytic lymphoma
2012 left adrenalectomy: Adrenal pseudocyst containing an EBV(+) siffuse large B-cell lymphoma with an activated B-cell phenotype along with lymphplasmacytic lymphoma seen in the extracapsular periadrenal soft tissue
Immunophenotype:
Positive: CD79a, PAX5, Bcl-6, MUM-1, Bcl-2, EBER, Kappa, MIB-1 (100%)
Negative: CD20, CD3, CD2, CD5, CD10, CD23, CD30, CD68, ALK-1, MNF116, Melan A, Inhibin, S-100, GFAP, Chromogranin, synaptophysin, CD56, Brachyurea
Cytogenetics: ·MYC not rearranged; 2-3 copies MYC (8q24)
·IGH/BCL2 negative; 2-3 copies BCL2 (18q21)
·BCL6 not rearranged; 2-4 copies BCL6 (3q27)
Molecular studies: IGH gene rearrangement studies were attempted on both the 2009 cyst excision as well as the subsequnet adrenalectomy specimen. However DNA quality was poor in both and no definate conclusion could be arrived at.
Proposed diagnosis: ·Microscopic EBV(+) diffuse large B-cell lymphoma arising in an adrenal pseudocyst.
·Activated B-cell phenotype.
·In the context of the previous lymphoplasmacytic lymphoma, is most likely to represent secondary transformation rather than a de novo tumour.
Interesting feature(s) of submitted case: ·2 cases of localized, microscopic DLBCL have been reported within pseudocysts 1. ·EBV(+), activated B cell phenotype. ·detected incidentally and were de novo tumours. ·one in adrenal pseudocyst, other in para-testicular pseudocyst. ·not associated with much chronic inflammation. ·both patients had favourable outcome.
·Similar cases have been reported in association with ·renal pseudocyst 2 ·splenic false cyst 3 ·Hydrocele 3 ·atrial myxoma 3 ·metallic implant wear debris 3 ·prosthetic heart valves ·synthetic vascular Dacron grafts surgical mesh implant 4.
·These were de novo tumours and positive for Epstein–Barr virus. · ·Loong et al support the hypothesis that the lymphoma has arisen in a setting of 'local immuno-deficiency' as a result of long-standing chronic inflammation in an enclosed space, characteristic of diffuse large B-cell lymphoma associated with chronic inflammation3. · ·'The pseudocyst represents a closed space and may prevent a cytolytic response to EBV-infected cells, thus resulting in local immunodeficiency which may be most important for pathogenesis' However, in our case, in the context of the previous LPL, the DLBCL is most likely to represent secondary transformation rather than a de novo tumour.

EAHP18-LYWS-153

Testicular Lymphoma

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Case description: An 82 year old male presented with bilateral, painless testicular enlargement. Imaging studies showed masses in bilateral testicles with distinct tumors measuring 4.5 cm (right) and 2.7 cm (left) in maximum dimension. These masses were gray pink, soft, and distinctly demarcated from adjacent uninvolved testicular tissue.
Biopsy fixation details: 10% NBF
Frozen tissue available: No
Details of microscopic findings: Cut sections of tumor tissue show diffuse sheets of abnormal lymphocytes. These are moderately pleomorphic and large in size. Frequent large cells have a single prominent nucleolus. The cells have delicate, granular nuclear chromatin with small amounts of pink cytoplasm. There are relatively frequent very large abnormal cells and occasional multinucleated tumor cells. Frequent mitotic figures and apoptotic bodies are seen.
Immunophenotype: The immunophenotype is as follows: positive staining for CD20, CD5, BCL2, MUM1, and FOXP1. Proliferation rate by Ki67 – 70%. Expression of P53 – 60%; CMYC – 30%. Partial weak expression for BCL6 (15%) and OCT4 (30%, weak, focal). Positive for OCT2 (strong, uniform, 100%). There is no staining for CD10, cyclin D1, GCET1, LMO2, SALL4 or PD-L1 (22C3).
Cytogenetics: FISH studies for IGH/BCL6, MYC, IGH/MYC and IGH/BCL2 are negative.
Molecular studies: None performed.
Proposed diagnosis: Diffuse large B cell lymphoma, CD5 positive, primary testicular with OCT-4 expression
Interesting feature(s) of submitted case: Features of note in this case are the presence of CD5 expression, non-germinal center phenotype and expression of OCT4. This combination of findings has been previously reported (see abstract below). The expression of OCT4 is unlikely to represent cross reaction with OCT2, due to the discordance of expression rate.

In contrast to many PT-DLBCL, this lymphoma does not express PD-L1.

Williams AS, Shawwa A, Merrimen J, Dakin Haché K. Expression of OCT4 and SALL4 in Diffuse Large B-cell Lymphoma: An Analysis of 145 Consecutive Cases and Testicular Lymphomas. Am J Surg Pathol. 2016 Jul;40(7):950-7. doi: 10.1097/PAS.0000000000000648.

EAHP18-LYWS-178

Primary testicular diffuse large B-cell lymphoma with MYD88 mutation and interesting cell of origin result

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Case description: A 57-year-old male presented with a hard lump in the left testicle. No lymphadenopathy or B symptoms. Left orchiectomy was performed and diagnosed as diffuse large B-cell lymphoma (DLBCL). Bone marrow biopsy was negative for involvement by lymphoma. PET scan was negative for other lesions. A lumbar puncture was performed and CSF was negative. He underwent 6 cycles of MR-CHOP followed by a course of radiation therapy to the opposite testicle, 30 Gy in 15 fractions and remains disease free.
Biopsy fixation details: Formalin.
Frozen tissue available: No.
Details of microscopic findings: The testicular parenchyma is extensively infiltrated by an abnormal population of large lymphocytes growing in a diffuse pattern.
Immunophenotype: Positive: CD20, CD10, and BCL6. Negative: CD3, CD5, CD23, BCL2. Ki67 is 70%.
Cytogenetics: FISH negative for MYC, BCL2, and BCL6 translocations.
Molecular studies: Positive for MYD88 L265P. Lymph2Cx cell of origin gene expression profiling (GEP) showed unclassifiable subtype.
Proposed diagnosis: Primary testicular DLBCL; germinal center B-cell (GCB) subtype by Hans algorithm, “unclassifiable” by Lymph2Cx assay; negative for MYC rearrangement; positive for MYD88 mutation.
Interesting feature(s) of submitted case: This is an interesting and classic case of primary testicular DLBCL, found to have a MYD88 L265P mutation. MYD88 mutations have been described in approximately 70% of primary testicular DLBCL, with similar rates seen in primary CNS DLBCLs. Together these represent DLBCLs occurring in immune-privileged sites. Intriguing site-specific variation in MYD88 mutation prevalence exists amongst DLBCLs, with these sites showing much higher rates of positivity. Interestingly, these “immune sanctuary” sites are also known to have poor response to therapy, and high risk of CNS relapse. The finding of high rate of MYD88 (and CD79B) mutations support a pathophysiology for these tumors distinct from DLBCLs at other sites, and raise possibilities for the future of targeted therapy in this disease.

This case is also interesting because of its cell of origin (COO) results. CD10 expression and GCB subtype by the Hans algorithm is uncommon in testicular DLBCL. Additionally, MYD88 mutations are enriched in DLBCLs of the activated B-cell (ABC) subtype in accordance with activation of B-cell receptor signaling and NF-kB pathways which drive these lymphomas. This lymphoma was diffusely positive for CD10, leading to a Hans algorithm classification of GCB. Perhaps not surprisingly, the Lymph2Cx GEP result was “unclassifiable” suggesting that this case does not fit neatly into either ABC or GCB subtype and was likely misclassified based on the Hans algorithm.

EAHP18-LYWS-183

Fibrin-associated diffuse large B-cell lymphoma arising in association with an abdominal aortic aneurysm

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Case description: The patient is a 74-year-old male with a history of hypertension, hyperlipidemia and coronary artery disease who presented with a six-month history of persistent flank pain and 20 kg weight loss. Radiographic exam demonstrated a rapidly expanding abdominal aortic aneurysm (AAA), PET positive, with extensive mural thrombus that extended into both renal arteries and the superior mesenteric artery. Patient underwent open AAA repair.
Biopsy fixation details: Arterial wall and thrombus from aorta and renal arteries, 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: There is a very focal proliferation of large atypical lymphoid cells with irregular nuclear contours within the thrombus, accompanied by extensive fibrinoid material and necrotic tumor cells. The adjacent arterial wall contains a mixed acute and chronic inflammatory infiltrate.
Immunophenotype: The tumor cells are CD20-positive and are diffusely EBV-positive (EBV-ISH).
Cytogenetics: Not done.
Molecular studies: Not done.
Proposed diagnosis: Fibrin-associated diffuse large B-cell lymphoma.
Interesting feature(s) of submitted case: Similar to most previously reported cases of fibrin-associated diffuse large B-cell lymphoma, this patient has had an excellent clinical outcome so far. He received six cycles of R-CHOP and has been in clinical remission for 4.5 years. Most prior cases of fibrin-associated diffuse large B-cell lymphoma of the cardiovascular system have arisen in association with foreign graft material, whereas the present case arose within the patient's native vasculature.

EAHP18-LYWS-184

Extranodal NK/T-cell lymphoma, nasal type, involving testis and central nervous system

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Case description: A 50-year-old previously healthy gentleman presented with polyradiculopathy including several cranial nerve palsies, progressive lower extremity weakness and saddle anaesthesia. MRI showed robust leptomeningeal/intradermal enhancement involving the lumbar spine, conus medullaris, and distal thoracic spinal cord with continued enlarged intrathecal nerve roots and right L5 nerve root in its neural foramen. PET scan also revealed moderate to intense FDG uptake in the right testicle, in additional to the distal spinal canal and some nerve roots. Right orchiectomy and lumbar puncture were performed.
Biopsy fixation details: 10% buffered formalin.

Frozen tissue available: No.
Details of microscopic findings: Histologic examination from testis showed testicular interstitium was diffusely infiltrated by atypical lymphocytes with intermediate to large nuclei, very irregular nuclear contours, vesicular chromatin, and distinct nucleoli. An angio-centric and angio-destructive pattern was apparent. Numerous mitotic figures were noted.
Immunophenotype: Flow cytometric immunophenotyping of the testis showed the neoplastic cells (82% of total analysed events) were positive for CD2, CD16, CD56 (uniform), CD94 (uniform), NKG2A (uniform), and they were negative for sCD3, CD4, CD5, CD8, CD57, TCR-gamma/delta, as well as killer-cell immunoglobulin-like receptor (KIR) express such as CD158a, CD158b, and CD158e (p70). Immunohistochemical studies revealed the neoplastic cells had cytoplasmic staining for CD3, and they were diffusely positive for Epstein-Barr virus encoded RNA (EBER), with Ki-67 proliferation index of 80%. Flow cytometric analysis of the cerebrospinal fluid revealed a distinct population of NK/T-cells with the same immunophenotypic features as those in the testis.
Cytogenetics: None
Molecular studies: None
Proposed diagnosis: Extranodal NK/T-cell lymphoma, nasal type.
Interesting feature(s) of submitted case: Extranodal NK/T-cell lymphoma commonly involves upper aerodigestive tract, less commonly gastrointestinal tract, testes and soft tissue, and rarely central nervous system. This is a classic case of extranodal NK/T-cell lymphoma, nasal type, interestingly, with two immune-privileged sites of involvement: testis and central nervous system. The advanced-stage disease (stage IV) and high Ki-67 proliferation index indicate significant unfavorable prognosis.

EAHP18-LYWS-196

Alk positive, CD 30 positive diffuse large B cell lymphoma, A case report

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Case description: A-63 year old female, presented with a chief complaint of mass in the axillar region for 2 months. The thorax x-ray was unremarkable, no mass in the mediastinum. The ultrasound of upper and lower abdomen also showed no abnormality. The lymphnode ultrasound revealed multiple suspicious lymphadenopathy in the right upper jugular, both axilla and inguinal region sized 0,5 cm to 3 cm.
Biopsy fixation details: The tissue was fixed by 10% buffer formaline
Frozen tissue available: No frozen tissue available
Details of microscopic findings: HE staining from the axillar mass biopsy showed sinusoidal growth pattern, composed of large atypical cells, round to oval nuclei, pleomorphic, and prominent nucleoli, with some large bizzare cells mimicking hallmark cells, and we proposed it as metastatic carcinoma with differential diagnosis of Anaplastic Large Cell Lymphoma
Immunophenotype: On immunohistochemical staining, all cells showed strong positivity with CD45 and negative for cytokeratin. CD 20 was diffusely positive, CD 30 was strongly positive in some of the cells. ALK was positive in all cells, with granular pattern in the cytoplasmic areas. This tumor also showed high index proliferation of Ki-67 (60%). Staining for CD3 and CD 138 was negative
Cytogenetics: No cytogenetic studies were performed
Molecular studies: No molecular studies were performed
Proposed diagnosis: ALK positive CD 30 positive Large B Cell Lymphoma
Interesting feature(s) of submitted case: The staining pattern was uncommon for ALK-positive Large B Cell Lymphoma which is should be lack of B cell marker and weak or negative for CD 45 and CD30 and also have plasmablastic differentiation with CD 138 positive. [1,2,3,4] We also excluded the Anaplastic Large Cell Lymphoma because of the strong positivity of CD 20. In view of the strong CD 20 (B-cell marker) positivity along with CD30 and ALK positivity, a diagnosis of ALK positive, CD 30 positive Diffuse Large B Cell Lymphoma was made

EAHP18-LYWS-213

Central nervous system involvement by systemic T-cell lymphoma with features of lymphomatosis cerebri

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Case description: 36 year old woman with a history of IgA nephropathy status post-renal transplant in 1995, presented with multiple pulmonary nodules in June, 2017. Lung wedge biopsies showed T-cell lymphoproliferative disorder with cytotoxic profile ($CD3^+/CD8^+$/ Granzyme $B^+/CD56^-/CD57^-/EBER^-$) (differential diagnosis included peripheral T-cell lymphoma, not otherwise specified and post-transplant lymphoproliferative disorder). CT abdomen, pelvis, and head was negative for malignancy. Bone marrow examination was negative for lymphoma. Review of the peripheral blood smear showed normal leukocyte count without lymphocytosis. Aspirate smear differential count showed 9% lymphocytes. Patient was treated with CHOP. She presented with difficulties in focusing eyes in November, 2017. Brain MRI showed multifocal areas of cortical/subcortical hyperintensities involving both frontal lobes, both hippocampi, left insula, corpus callosum, left thalamus, and brainstem with associated areas of restricted diffusion, and patchy gyriform enhancement of the involved cortices.
Biopsy fixation details: Brain biopsy was fixed in formalin.
Frozen tissue available: NA
Details of microscopic findings: Review of the sections showed increased number of small to medium sized lymphocytes some with elongated, curvy nuclei that are distributed singly or making small loose clusters. Increased number of microglial cells and scattered enlarged astrocytes were also noted consistent with microglial activation and reactive astrocytosis.
Immunophenotype: The neoplastic cells were positive for CD3, CD8, granzyme B, and focally p53 (30-40%). They were negative for CD20, CD4, and CD57. GFAP stain demonstrated numerous glial cells, some of which were enlarged. CD163 stain demonstrated numerous microglial cells with extensive cytoplasmic projections. The cells were negative for IDH1 stain. EBER was performed and the cells were negative. GMS stain does not demonstrate any fungal microorganisms.
Cytogenetics: NA
Molecular studies: Monoclonal T-Cell receptor gamma (TCRG) and beta (TCRB) chain gene rearrangements were detected by PCR analysis.
Proposed diagnosis: T-cell lymphoproliferative disorder with cytotoxic phenotype.
Interesting feature(s) of submitted case: This is an unusual case of systemic T-cell lymphoma involving central nervous system diffusely without mass formation. Imaging studies showed no intracranial mass but multifocal areas of hyperintensities. The neoplastic cells, in contrast to a typical T-cell lymphoma, do not form a discrete mass, but rather show a single cell type diffuse infiltration. With the previous diagnosis of T-cell lymphoproliferative disorder in the lung, this most likely represents the brain involvement by systemic lymphoma. This pattern has been reported previously as "lymphomatosis cerebri (LC)".
Primary central nervous system lymphoma (PCNSL) that diffusely infiltrates brain parenchyma rather than presenting as a discrete lesion is referred to as LC. Due to the nonspecific clinical and neuroimaging features, differential diagnosis includes gliomatosis cerebri, central nervous system infections, and inflammatory, toxic, and metabolic disorders. Therefore, this diagnostic dilemma can lead to delay in the diagnosis of LC and its appropriate treatment. Majority of the patients with LC had a diagnosis of diffuse large B-cell lymphoma, and rarely low grade B-cell lymphoma or T-cell lymphoma. This term does not define a distinct disease entity, so it should not replace the specific diagnosis. However, we should be aware of this pattern of brain involvement by lymphoma to prevent the delay of the diagnosis and appropriate treatment.

EAHP18-LYWS-262

Initial CNS presentation of a small B-cell neoplasm with plasmacytic differentiation

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Case description: The patient is a 79 year old woman with a history of stroke 15 years ago and slowly progressive left sided weakness over the last 7 years. A CT of the brain identified no mass lesions, but an MRI demonstrated patchy enhancement in the right frontal and anterior parietal lobes. The radiologic findings were interpreted as suspicious for an intravascular lymphoma versus granulomatous angiitis. Physical exam revealed no adenopathy or organomegaly. A biopsy was obtained from the right frontal lobe. Following diagnosis, additional staging studies are in progress.
Biopsy fixation details: Neutral buffered formalin.
Frozen tissue available: No.
Details of microscopic findings: The histologic sections demonstrated a perivascular infiltrate of small lymphocytes, plasmacytoid cells and plasma cells. Mott cells and Russell bodies were present. A distinct lymphoid mass lesion was not identified. A medium sized vessel was noted to contain eosinophilic, hyalinized material and a Congo Red stain confirmed the presence of amyloid.
Immunophenotype: Immunohistochemical stains demonstrated the perivascular infiltrate to contain numerous CD20 positive, CD79a positive cells admixed with few CD3 positive cells. A CD138 stain highlighted a subset of the infiltrate. Kappa and lambda in situ hybridization stains showed the infiltrate to contain numerous kappa light chain restricted cells. A Ki67 stain showed <10% positive nuclei.
Cytogenetics: Not performed.
Molecular studies: Negative for MYD88 L265P by allele specific PCR.
Proposed diagnosis: Small B-cell neoplasm with plasmacytic differentiation (marginal zone lymphoma versus MYD88 L265P negative lymphoplasmacytic lymphoma).
Interesting feature(s) of submitted case:
1) Lymphomas presenting within the CNS are typically aggressive neoplasms, and small B-cell neoplasms with initial presentation at this site are rare. Furthermore, this neoplasm is difficult to classify by current WHO criteria.
2) The findings were initially suggestive of CNS involvement by lymphoplasmacytic lymphoma (i.e., Bing-Neel syndrome). However, Bing-Neel syndrome typically represents secondary involvement of the CNS in a patient with a prior history of systemic LPL, and initial presentation with a CNS lesion is rare. Furthermore, this case is negative for the MYD88 L265P mutation associated with >90% of LPL cases.
3) The alternative possibility of an extranodal marginal zone (MALT) lymphoma was also considered. MALT lymphomas of the CNS, however, are typically dural based and present with a distinct mass lesion, in contrast to the current case which was based in brain parenchyma without a distinct mass lesion.
4) On the basis of this index case, a review of small B-cell neoplasms with initial presentation in the CNS at our institution is currently underway. Results of this series will be available for further discussion.

EAHP18-LYWS-274

Primary vitreoretinal diffuse large B-cell lymphoma

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Case description: A 72 year old male, with a past medical history of pulmonary embolism and deep vein thrombosis, presented in May 2017with blurry vision and sudden onset of hundreds of floaters in his right eye. He did not have any prior history of retinal detachment, trauma or surgery to the eyes.
Ophthalmic examination of the right eye revealed a posterior vitreal detachment with increased vitreous cells but no hemorrhage or other lesions. Ophthalmic examination of the left eye only showed trace vitreous cells. Physical examination revealed no lymphadenopathy.
A full rheumatologic and infectious workup was negative. The patient was observed for 4 months, during which his symptoms slowly progressed to involve his left eye (developed a posterior vitreous detachment and small retinal break on subsequent examination). A right diagnostic vitrectomy was performed.
Brain magnetic resonance imaging (MRI) showed no significant abnormality. Positron emission tomography (PET) scan was also negative. Bone marrow biopsy showed no evidence of lymphoma. Cerebrospinal fluid cytology was negative for malignancy.
The patient was initiated on alternating injections of intraocular rituximab and methotrexate in the right eye, with observation of the left eye. He reports significant improvement in the right eye vision on follow up in Dec 2017.
Biopsy fixation details: 11 ml of vitreous and 100 ml of vitreous washing. The fluids were pink and slightly turbid. They were submitted for cell block preparation in 10% neutral buffered formalin.
Frozen tissue available: Not available.
Details of microscopic findings: Occasional large cells with irregular nuclear contours, vesicular chromatin, multiple nucleoli and moderate amounts of cytoplasm. Background of acellular vitreous and a polymorphous infiltrate consisting of few small lymphocytes, plasma cells and histiocytes.
Immunophenotype: The large atypical lymphocytes are CD20 positive. Rare reactive CD3 positive cells are seen. No additional phenotyping could be performed due to the scant cellularity.
Cytogenetics: Not available.
Molecular studies: Negative for the MYD88 L265P mutation by allele-specific polymerase chain reaction (PCR) on right eye vitreous paraffin-embedded tissue.
Proposed diagnosis: Vitreous, right eye, aspiration: Large B-cell lymphoma.
Interesting feature(s) of submitted case: This is a rare case of vitreoretinal diffuse large B-cell lymphoma (VRL), confined to the eyes with no central nervous involvement (CNS). Primary VRL are rare, and the large majority of patients eventually develop CNS spread [1]. Our patient unusually has disease limited to the eyes on continuous follow up for more than 6 months, and also lacks a MYD88 mutation- which is seen in greater than 80% of primary VRL [2]. They are observed at a similarly high frequency in PCNSL [3], leading some to conclude that primary VRL and PCNSL represent the same entity [4]. Despite no significant relationship found between MYD88 mutational status and CNS involvement [4], there is no data in the current literature comparing the survival of MYD88 L265P vs. MYD88 WT primary VRL or PCNSL. MYD88 L265P mutations have been found to be associated with more severe disease in systemic DLBCL [5]. It is unclear if our patient's excellent course and prognosis is related to the absence of this mutation.
[1]Chan CC et al. Oncologist. 2011;16(11):1589-1599
[2] Raja H et al. Retina. 2016 Mar;36(3):624-8
[3] Gonzalez-Aguilar A et al. Clin Cancer Res 2012;18(19):5203-5211
[4] Bonzheim I et al. Blood. 2015 Jul 2;126(1):76-9
[5] Fernandez-Rodriguez C et al. Leukemia 2014;28:2104–2106

EAHP18-LYWS-280

Breast implant associated EBV positive diffuse large B cell lymphoma associated with chronic inflammation

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Case description: The patient is female and was 69 years old at the time of resection.
The patient had bilateral breast augmentation with subglandular implants (Allergan 410 475cc) in 2007. In 2011 there was bilateral capsulectomy and implants exchange with right full capsulectomy and left partial capsulectomy (Allergan textured 605cc). In July 2016 there was a further bilateral capsulectomy and implants exchange with bilateral mastopexy - right full capsulectomy, left partial capsulectomy (Polyurethane 395cc). A preoperative mammogram had shown a right capsular contracture.

The submitted material is from the right capsulectomy.

A bone marrow aspirate and biopsy was negative for lymphoma.

Following diagnosis the patient was treated with 3 cycles of R-CHOP with intrathecal prophylaxis to complete response with no evidence of disease on CT
Biopsy fixation details: Formalin
Frozen tissue available: No
Details of microscopic findings: Within the fibrous capsule there is a patchy infiltrate of partly degenerate large cells with abundant cytoplasm and large pleomorphic nuclei.
In the background there is a chronic inflammatory reaction with a patchy dense infiltrate of plasma cells and scattered reactive lymphoid follicles.
Immunophenotype: Positive
CD19, CD20, CD22, CD79a MUM1, bcl-2, EBER. Lambda light chain restriction.
Negative:
CD10, bcl-6, CD2, CD3, CD5, CD7, HHV-8.
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: EBV positive diffuse large B cell lymphoma associated with chronic inflammation
Interesting feature(s) of submitted case: This is an unusual case of large B cell lymphoma associated with breast implant rather than the typical anaplastic large cell lymphoma ALK negative that is the more common implant associated lymphoproliferation. This is also an unusual site for an inflammation associated lymphoma.

EAHP18-LYWS-292

Space-occupying cerebral lesion in a patient on azathioprine treatment

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Case description: A 51 year old woman presented with a two week history of dizziness, morning headache and lethargy. Imaging showed a space-occupying lesion in the basal ganglia, thought to be a glioblastoma, which was biopsied.
The history of iatrogenic immunosuppression was not known initially when the case was diagnosed in another institution as diffuse large B-cell lymphoma (EBV testing had not been performed), thought to be primary CNS large B-cell lymphoma. The patient was referred to our institution for treatment of 'primary CNS large B-cell lymphoma' and she then commenced the first cycle of chemotherapy as part of the MATRIX protocol but this was stopped following review of histology and revision of diagnosis . The patient had a past medical history of autoimmune hepatitis, for which she was taking long-term azathioprine. EBV PCR was positive with a titre of 898 IU/L. Azathioprine was discontinued and the patient was commenced on weekly rituximab to which there has been a good clinical and radiological response.
Biopsy fixation details: Unknown as external material, not processed in local laboratory.
Frozen tissue available: No
Details of microscopic findings: There is a polymorphous population of lymphoid and plasma/plasmacytic cells infiltrating brain parenchyma, ranging in size from small to large and demonstrating a focally perivascular distribution. The lymphoplasmacytoid infiltrate includes small and medium sized lymphoid cells, scattered large cells and many plasmacytoid cells that range from small to medium and scattered large plasmacytoid cells and some mature plasma cells.
Immunophenotype: The lymphoplasmacytoid/plasmacytic infiltrate is positive for CD79a. The lymphoid cells and some plasmacytoid cells express CD20 and the plasma cells are positive for CD138. They are negative for CD5 and cyclin D1. The entire polymorphous B cell and plasmacytic population are positive by in situ hybridisation for EBV and demonstrate kappa light chain restriction. Kappa positive Dutcher bodies are noted. CD3 highlights a variable number of T-cells in the background. The Ki67 proliferation index is moderate.
Cytogenetics: Not applicable
Molecular studies: Amplification of target genes for PCR for clonality studies failed due to poor DNA quality.
Proposed diagnosis: Iatrogenic (azathioprine)-associated EBV positive, clonal polymorphic B-lymphoproliferative disorder
Interesting feature(s) of submitted case: This case highlights the value of relevant clinical information and also emphasises the importance of appreciating the polymorphous nature of the lymphoplasmacytoid infiltrate which is against a diagnosis of large B-cell lymphoma and should prompt testing for EBV (even if not performed at the outset) and further questioning of the clinicians for a likely source of immunosuppression in order to prevent misdiagnosis and its consequences.

EAHP18-LYWS-326

HHV8 negative and EBV negative primary effusion lymphoma

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Case description: An eighty-one years old gentleman has medical history of congestive heart failure, coronary artery disease, and valvular heart disease status post mitral valve replacement and CABG more than 6 months ago. He developed progressive fatigue and dyspnea after surgery and was found recurrent pleural effusion which required multiple thoracentesis. Cytology laboratory recieved 1100 mul amber fluid for analysis. Further work up including CT san did not reveal any other lesions or lymphadenopathy; blood work was negative for HIV, Hep B, Hep C, HHV6 or HHV8. Bone marrow biopsy was negative for malignancies.
Biopsy fixation details: 10% buffered formalin.
Frozen tissue available: None.
Details of microscopic findings: The cytospin and cell block show numerous large atypical lymphocytes. The atypical lymphocytes contain large nuclei with open chromatin, irregular neclear contour, and multiple nucleoli. Binuleated or mulinucleated atypical forms are often seen. Mitoses are easily identified.
Immunophenotype: The atypical lymphocytes are positive for CD20, PAX-5, BCL-2, BCL-6, and MUM-1 (weak and focal); negative for CD10, CD138, CD3, CD45RO, HHV-8, pancytokeratin, and Calretinin. EBER in situ hybridization for EBV is negative. The proliferative rate by ki-67 is high (>90%).
Cytogenetics: FISH with break-apart probe for C-MYC gene rearrangement was negative.
Molecular studies: None.
Proposed diagnosis: HHV8 and EBV negative primary effusion lymphoma.
Interesting feature(s) of submitted case: In contrast to typical primary effusion lymphoma, this case is unusual due to the negative results of HHV8 and EBV; also the patient does have excellent response to R-CHOP and still is well alive in 3 years.

EAHP18-LYWS-344

Central nervous system dissemination of mycosis fungoides

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Case description: A 33-year-old woman, known since the age of 16 for atopic dermatitis, presented at the end of 2012 with multiple cutaneous plaques and nodules and peripheral lymphadenopathies. Two skin lesions (abdomen and forearm) were biopsied and diagnosed as mycosis fungoides (MF) and MF with large cell transformation (tMF). A lymph node biopsy showed dermatopathic changes without lymphoma (Stage IIB). Local therapy (UVB, PUVA and radiation therapy) and interferon were administered, leading to almost complete remission. In July 2015 she developed neurological symptoms (headache, epileptic crisis). Brain MRI detected seven cerebral lesions, suspicious for lymphoma. Two lesions were evaluated by stereotaxic biopsies. After a negative bone marrow staging biopsy, she was started on chemotherapy using MATRix regimen (methotrexate, cytarabine, thiotepa, without rituximab) followed by ICE (ifosfamide, carboplatine, etoposide) and brentuximab. Worsening clinical conditions finally lead to palliative care. The patient died in December 2015.
Biopsy fixation details: Formalin.
Frozen tissue available: Brain biopsy.
Details of microscopic findings: Skin biopsy (forearm, December 2012): diffuse dermal infiltration by predominantly large cerebriform lymphoid cells with high mitotic activity and focal epidermotropism, without small cell component.
Skin biopsy (abdomen, January 2013): atypical lymphoid infiltrate with epidermotropism, Pautrier abcesses.
Brain biopsies (right frontal and parietal, 2015): medium to large atypical lymphoid cells with cerebriform nuclei, somewhat anaplastic features and perivascular distribution.
Immunophenotype: Skin biopsy (forearm): CD2– CD3– CD5– CD4+/– CD7– CD30+ ALK– EMA– non-cytotoxic (perforin, granzyme B, and TIA-1 negative) tumor cells.
Skin biopsy (abdomen): CD3+ CD4+ CD8– CD30– tumor cells.
Brain biopsies: CD2– CD3+ CD5– CD7+ CD8– CD20– CD30+ ALK– EMA– EBV/LMP– TCR γ– TCR β-F1– tumor cells with an activated cytotoxic (perforin, granzyme B, TIA-1) immunophenotype and >80% Ki67 proliferative index. Faint CD4 expression on some tumor cells could not be ruled out.
Cytogenetics: Not done.
Molecular studies: Comparative T-cell clonality analyses of skin and brain biopsies showed an identical monoclonal TRG gene rearrangement in all four samples with one primer set (BIOMED-2 tube B, heteroduplex analysis). An additional TRG monoclonal rearrangement band was observed exclusively in the brain lesions (BIOMED-2 tube A), while a monoclonal TRB gene rearrangement was detected only in the skin specimens (BIOMED-2 tube C). Sanger sequencing of TRG-tube B amplification products, performed because of these only partially overlapping rearrangement profiles, demonstrated identical sequences in all four samples, indicating a common clonal origin.
Proposed diagnosis: Skin biopsy (abdomen): mycosis fungoides (MF).
Skin biopsy (forearm): MF with large cell transformation (tMF).
Brain biopsies (frontal and parietal, submitted for the workshop): **multifocal involvement by tMF.**
Interesting feature(s) of submitted case: CNS involvement by tMF is extremely rare, the most common sites of extracutaneous involvement being liver, spleen and lungs.
Substantial immunophenotypic differences were observed between the cutaneous and cerebral lesions, questioning the clonal relationship between the lymphoma in both localizations, and challenging the adequate classification of this CNS lymphoma as either progression of MF or a second lymphoma. While the patterns of TR gene rearrangements by standard electrophoresis were somewhat ambiguous, sequencing of the amplification products demonstrated identical sequences, consistent with MF progression in the brain.

EAHP18-LYWS-354

Primary diffuse large B cell lymphoma (DLBCL) of the thyroid with MHC class II transactivator (CIITA) abnormalities, loss of MHC Class II (MHCII) expression, and "immune excluded" phenotype.

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Case description: The patient is a 75-year-old male who presented in 01/2017 with progressive change in his voice and was found to have left vocal cord paralysis. Subsequent neck ultrasound and CT scan revealed a 7.8 x 4.9 x 4.1 cm mass in the left thyroid lobe with extension into the left paraglottic space and vocal cords, and enlarged right and left supraclavicular lymph nodes. Multiple fine needle aspirations were attempted but were non diagnostic. Near total thyroidectomy with left neck dissection were performed on 05/2017 at an outside institution, revealing DLBCL with extension into the surrounding soft tissues. The patient presented to our institution on 06/2017 for a second opinion.
Biopsy fixation details: Formalin.
Frozen tissue available: Consistent with lymphoma.
Details of microscopic findings: Histologic sections showed thyroid tissue with an atypical lymphoid infiltrate extending to the surrounding soft tissue and skeletal muscle. The infiltrate was composed of medium to large size lymphoid cells with irregular nuclei, vesicular chromatin, some with distinct nucleoli. Necrosis and frequent apoptotic bodies were seen. Areas of lymphocytic thyroiditis were present in the background.

Immunophenotype: Immunohistochemistry
The atypical lymphoid cells were positive for CD20, CD10 and BCL6; while negative for MUM1, BCL2, CD30, CD23, EBER-ISH, CMYC and Beta2 microglobulin. Cytoplasmic MHCI expression was retained, while MHCII and CIITA expression was lost. PD-1 and PD-L1 highlighted peritumoral immune cells with exclusion of the neoplastic infiltrate, so-called "immune excluded" phenotype. The proliferation index (Ki67) was 90%.
Flow cytometry was noncontributory due to decreased viability and non specific staining.
Cytogenetics: FISH analysis for CIITA was positive for rearrangement.
FISH analysis for PD-L1/2 locus, BCL6, MYC, MALT1, t(11;14) and t(14;18) was negative.
Molecular studies: The comprehensive genomic sequencing was performed using Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets platform (MSK-IMPACT HEME) (hybridization capture-based next-generation sequencing assay):
CIITA loss (Fold change: -1.3)
CIITA p.C618R

BRAF p.K601N
IDH2 p.R140Q
TET2 p.S835
TET2 p.S1525Vfs
B2M p.M1
CD274 p.C114Y
CDKN2Ap14ARF p.R4Sfs*56
MAP3K1 p.M1442L
MGA p.E1223K
NOTCH2 p.M2169T
P2RY8 p.P252S
PCBP1 p.N84T
ROBO1 p.T730M
SGK1 p.F122I
SGK1p.X146
SRSF2 p.P95H
SRSF2 p.P95R
TP63 p.R318C

Proposed diagnosis: DLBCL, germinal center immunophenotype (Hans algorithm).
Interesting feature(s) of submitted case: MSK IMPACT HEME NGS assay detected CIITA mutation and copy number loss. FISH assay confirmed rearrangement, which correlated with loss of CIITA and MHCII expression by immunohistochemistry.
CIITA is the master regulator of MHCII antigen presenting pathway. Loss of CIITA expression by mutations and other mechanisms has been reported in primary mediastinal large B-cell lymphoma and Classical Hodgkin lymphoma and it is believed this leads to reduction of MHCII surface expression, contributing to immune escape and adverse outcomes. This case shows that CIITA abnormalities are also seen in DLBCL arising in immune priviledged extranodal sites. In addition, the tumor shows architectural features of "immune excluded" phenotype described for solid tumors. These findings contribute to growing evidence implicating immune escape as a dominant oncogenic mechanism across B cell lymphomas, with potential implications for immune mediated therapies.

EAHP18-LYWS-359

Small lymphocytic lymphoma with interfollicular pattern of infiltration presenting in the Waldeyer's ring in a 36-year-old man

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Case description: The patient is 36 years-old male who is admitted with complaints such as difficulties in breathing in nights, snoring, mild dysphagia, and frequent tonsillary swelling for four years. It was diagnosed as lymphoid tissue hyperplasia in nasopharyngeal biopsy two years ago in an outside center. He had no B symptoms, hepatosplenomegaly or any chronic disease. The blood count of white cells was at the top of normal range ($10.1x10^9$/L, N: 4.5-$10.3x10^9$) with slight lymphocytosis (4. $1x10^9$/L, N: 1.3-$3.5x10^9$). LDH was normal (228 U/L, N: 0-248 U/L). Tonsillectomy and adenoidectomy were performed because of the presence of bilateral tonsillar hypertrophy and nasopharyngeal lymphoid hypertrophy detected in psychical examination. The right tonsil was 4.5x3.2x1.8 cm, the left one was 3.5x2.8x2 cm and both tonsils were appeared normal at gross examination except their large sizes. Cervical, axillary, and inguinal lymph nodes reaching up 2.3 cm were present. Bone marrow biopsy was not involved. The patient didn't take any medication. He was followed-up with active surveillance in the next 14 months and is doing well; number of white cells and lymphocytes in blood counts are almost same with those at the time of the diagnosis.
Biopsy fixation details: Formalin fixed paraffin embedded tissues
Frozen tissue available: No.
Details of microscopic findings: The architecture of the tonsils was not disrupted. Between crypts and lymphoid reactive follicles, some interfollicular areas were expanded by small lymphoid cell infiltration. These cells had small, round nuclei.
Immunophenotype: The neoplastic cells were positive for CD20, CD5, CD23, bcl-2, ZAP70, LEF1; and negative for CD10, TdT, bcl-6, CD28, cyclin-D1, and Sox-11 with a Ki-67 proliferation indexion of 20-30%.
Cytogenetics: Not done.
Molecular studies: Not done.
Proposed diagnosis: Small lymphocytic lymphoma with interfollicular pattern
Interesting feature(s) of submitted case: Tonsil and adenoid presentation of chronic lympocytic leukemia/small cell lymphoma (CLL/SLL) is very rare. In addition, interfollicular involvement in CLL/SLL is also rare and may create difficulties in diagnosis especially in extranodal areas. Third interesting feature of the case is the patient's young age which is unusual for CLL/SLL.

EAHP18-LYWS-363

Primary testicular Lymphoma (DLBCL) followed by primary CNS Lymphoma (DLBCL)

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Case description: A 42y old man presented with a scrotal mass (6.5cm). In the frozen section, a seminoma was diagnosed and lead to semicastration. In the definitive histology, a diagnosis of primary testicular DLBCL was established. Iliacal and paraaortic lymph nodes were involved (Stage IIAE, IPI low). The contralateral testis was not biopsied. The patient received 6cy CHOP/Rituximab with intrathecal prophylaxis.
5.5 years later, vitrectomy of the right eye was performed but tough atypical lymphocytes were seen, no lymphoma diagnosis could be established.
Another 5 months later, a thalamic mass (4.2cm) was diagnosed as primary CNS DLBCL (Stage IE) on a biopsy. The patient received 7cy Rituximab, 4cy Methotrexate and 2cy AraC high-dose followed by autologous SCT. In the last follow-up, 16 years after inital manifestation, he is free of disease.
Biopsy fixation details: buffered formalin (4%)
Frozen tissue available: no
Details of microscopic findings: 1. testis: sheets of large polygonal cells
2. CNS: sheets of large polygonal cells
Immunophenotype: 1. testis: CD20+, CD3 -, CD5-, Mib1 85%, BCL10-, BCL6+ (weak), CD10-, COO: non-GCB
2. CD20+, CD3-, Mib 1 95%, BCL6+, BCL2-, CD10-, c-MYC-, LMO2+, GCET1-, Foxp1+, MUM1-, COO: non-GCB
EBER nd
Cytogenetics: nd
Molecular studies: tDLBCL:1. chr6 gene PIM1 (Coding c.373C>T, allel frequency 46.3), missense 2. chr12 gene KMT2D (Coding c.982G>A, allel frequency 39.9), missense, 3. chr6 gene PIM1 (Coding c.454>G, allel frequency 39.3), missense, 4. chr6 PIM1 (Coding c.361G>A , allel frequency 23.8), missense
CNS DLBCL: 1. chr6 gene TNFAIP3 (Coding c.292_293insACTT, allel frequency 13.7%) frameshift Insertion, 2. chr12, gene KMT2D (Coding c.11592C>G, allel frequency 5.9%) missense
Proposed diagnosis: 1. primary extranodal diffuse large B cell lymphoma of the testis
2. primary diffuse large B cell lymphoma of the CNS
Interesting feature(s) of submitted case: 1. A lymphoma can be difficult to diagnose on frozen sections of the testis in middle aged men, as germ cell tumors and hematolymphoid tumors can have a similar morphology. Still, only germ cell tumors need a resection.
2. Both tumors belong to lymphomas of immune-privileged sites. This case represents an example of testicular lymphoma followed by CNS lymphoma, which is wellknown from ltiterature. Tough both lymphomas in general have a worse prognosis than nodal DLBCL, the patient is still alive without disease.
3. Array CGH and NGS panels (lymphoma custom panel) showed two different, clonally not related tumors.
This case has been published as Case 17 in Leukemia (2016) 30, 2385–2395; doi:10.1038/leu.2016.135

EAHP18-LYWS-396

Possible Bing-Neel Syndrome with IgG producing LPD and MYD-88 L265 mutation

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Case description: 59 year old woman with background history of low grade CD5 -, CD10 – Lymphoproliferative disorder accompanied by IgG kappa paraprotein; differential is lymphoplasmacytic lymphoma versus marginal zone lymphoma. Diagnosis made pre discovery of MYD 88 mutation in 2014 and treated with RFM chemotherapy x 3 cycles. Presented in November 2017 with several months history of headache, increasing photosensitivity and sudden onset of binocular vision loss, which resolved after a few seconds. No speech changes, sensory deficits or any weakness in any particular limb.
Biopsy fixation details: Paraffin embedded trephine
Frozen tissue available: Not available
Details of microscopic findings: This moderately hypercellular trephine biopsy shows a significant small lymphoid infiltrate comprised predominantly of CD20 positive cells distributed in heavy interstitial, diffuse and vaguely nodular locations. Plasma cells are very few and there are Dutcher bodies. Many of the lymphocytes show plasmacytic differentiation. The differential diagnosis lies between IgG producing Lymphoplasmacytic Lymphoma and Marginal Zone Lymphoma. Disease burden is estimated at approximately 70-80%.The awaited PCR for MYD88 L265P mutation is likely to add further information regarding the exact diagnosis.
Immunophenotype: Immunophenotyping on the CSF sample showed taht B cells are increased at 39% of lymphoid cells with Kappa light chain restriction and weak expression, suggestive of involvement by low grade B cell lymphoma
Cytogenetics: Not available
Molecular studies: MYD88 L265P mutation: positive

Proposed diagnosis: Bing-Neel Syndrome with IgG producing LPD and MYD-88 L265 mutati
Interesting feature(s) of submitted case: IgG not IgM producing waldenstrom macroglobulinaemia; diagnosis of WM confirmed on MYD88 L265P mutation analysis
CNS involvement by LPL is consistent with the rare Bing-Neel syndrome

EAHP18-LYWS-397

Primary anaplastic large cell lymphoma of central nervous system

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Case description: An immunocompetent 13-year-old child presented in july 2010 with 2 weeks history of headache that wakes up at night and does not calm with conventional analgesia, with vomiting and photophobia, afebril, and episode of tonic crisis with cephalic deviation. Imaging studies showed in TC and MR: left temporal intraparenchymatous poorly defined lesion of 3 cm. size, with marked perilesional edema that displaces structures of median line to the right, signs of subfalcial herniation and transtentorial descending herniation. Thoracoabdominal TC scan and spinal MR not found lymphadenopathies or extranodal involvement, howeves bone scintigraphy showed uptake in right femoral diaphysis. Craniotomy and lesion excision were performed. After diagnosis treatment was done according to SHOP LNH98b (SFOP LMB89) group C. The regimen was modifying because complications treatment related. The patient was in complete remision at the end of 2017.
Biopsy fixation details: 10% buffered formalin fixed and paraffin-embedded.
Frozen tissue available: not-available.
Details of microscopic findings: Extensive tumoral necrosis background with a viable large-sized quite monomorphic cells, predominantly round-oval nuclei, finely clumped chromatin with small basophilic nucleoli and broad cytoplasm. The tumor cells formed cohesive aggregates/sheets with prominent perivascular infiltration. Occasionally horseshoe-shaped nuclei ("hallmark-cells") and mitosis figures were observed. Presence of numerous histiocytes and plasmatic cells accompanying.
Immunophenotype: Immunohistochemical stains demonstrate CD30 strongly and diffuse positive, CD3 and CD7 positive, with partial loss of CD2, CD5 and CD4, with alteracion CD4/CD8. The ALK stain was positive cytoplasmic and nuclear. CD20, CD79a, PAX-5, bcl-2, CD10, bcl-6, CD23, CD56, granzyme-B, EMA, TdT, CD15 and latent membrane protein of Epstein-Barr virus (LMP-1) were negative in proliferating cells. EBV EBERS in situ hybridation was negative. Plasmatic cells showed CD79a, CD138, MUM-1 and light chain positivity. Rate of proliferation Ki-67 greater than 60%.
Cytogenetics: not-done.
Molecular studies: PCR: clonal rearragement of TCR gamma (two clonal products of 205bp and 208 bp).
Proposed diagnosis: Primary anaplastic large cell lymphoma (ALCL) of central nervous system, ALK-positive.
Interesting feature(s) of submitted case: ALCL central nervous system (CNS) involvement is very rare and is limited to case reports and small case series. ALCL of CNS has been found to be more aggressive than difusse large B-cell lymphoma or systemic ALCL. However a better outcome was associated with young age, unifocal tumor, ALK positivity and lack of necrosis.

EAHP18-LYWS-423

Primary Testicular Diffuse Large B-Cell Lymphoma, Non-Germinal Center-like, with Coexistence of MYD88 and CD79B Gene Mutations

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Case description: A 76-year-old male presented in 2004 with marked shortness of breath and fever. Chest X-Ray and CT scan showed bilateral pleural and pericardial effusions. Bilateral thoracentesis and pericardiocentesis were done. The findings of morphology, flow cytometric analysis (FCA) and immunohistochemistry(IHC) of pleural and pericardial fluid were identical Following a diagnosis of large B-cell lymphoma, CT and PET scan of chest, abdomen and pelvis showed no abnormality. Bone marrow was uninvolved. Physical exam revealed enlarged right testis. Right testis was resected. The testis was ovoid, firm to hard, measured 6.2 x 5.1 x 4.0 cm, and had fish flesh-like cut surface. A diagnosis of DLBCL was made based on FCA, histomorphology and IHC. He was treated with 6 cycles of R-CHOP and intrathecal methotrexate. In 2012, he developed massive generalized lymphadenopathy and left axillary lymph node (LN) was excised and submitted fresh to pathology. LN was oval, measured 2.5 x 2.3 x 1.7 cm and had fish flesh-like cut surface. Most of the tissue was fixed in 10% Neural Buffered Formalin and a small piece was submitted for flow cytometry. A diagnosis of DLBCL, non-GC-like was made. There were morphologic and immunophenotypic similarities between testicular and nodal DLBCL. His condition rapidly deteriorated with high grade fevers and respiratory difficulty. He did not want to be on ventilator, did not want any treatment for lymphoma and was sent to hospice where he passed away in a few days.
Biopsy fixation details: 10% Neutral Buffered Formalin
Frozen tissue available: No
Details of microscopic findings: Testicular lymphoma showed subtotal effacement of testis by a diffuse infiltrate of medium-sized and large lymphoid cells with high N:C ratio, prominent nucleoli and many mitotic figures. Left axillary lymph node in 2012 showed morphologic features similar to those in the testis.
Immunophenotype: Positive IHC stains in the testis: CD20, CD79a, BCL2, BCL6, MUM1, MYC, KI67 (~99%); **Negative IHC stains in the testis**: CD3, CD5, CD10, CD30, BCL1, EMA, and EBV-LMP1. ISH for EBER was negative; **Positive IHC stains in the lymph node**: CD20, CD79a, BCL6, MUM1, MYC, KI67 (~99%); **Negative IHC stains in the lymph node**: CD3, CD5, CD10, CD30, BCL2, BCL1, EMA, and EBV-LMP1. **ISH for EBER** was negative in both the testis and the lymph node; **Positive Flow Cytometry Markers in Testis**: CD20, CD19, CD22, FMC-7, HLA-DR, sLambda; **Positive Flow Cytometry Markers in Lymph Node:** CD20, CD19, FMC-7, HLA-DR, sLambda
Cytogenetics: Not done
Molecular studies: FISH on Testicular Lymphoma: 3q+; no evidence for double or triple hit lymphoma; **Next-Generation Sequencing using 128-gene panel:** Pathogenic mutations are detected in MYD88, CD79B and PIM1 genes
Proposed diagnosis: Primary Testicular Diffuse Large B-Cell Lymphoma, Non-Germinal Center-like, with Coexistence of MYD88 and CD79B Gene Mutations
Interesting feature(s) of submitted case: 128-gene NGS panel revealed coexistence of MYD88 gene mutation (at position L265P) and CD79B gene mutation in the primary testicular lymphoma. This co-existence has been described in primary testicular lymphoma.[1] It is very likely that MYD88 signaling cooperated with B-cell receptor signaling by CD79B to maintain survival of our non-GC-like (ABC type) primary testicular DLBCL.[2]

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EAHP18-LYWS-434

Primary DLBCL of the iris in a patient with CLL

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Case description: 70-year-old female with a history of CLL, stable without treatment, presented with a tumour of the iris known for 1 year, clinical suspicion of CLL infiltrate. No response to systemic steroid therapy, an outside biopsy was insufficient for diagnosis. Resection of the iris tumour (submitted specimen). The patient is otherwise in good health. Follow-up: Patient currently has received 4 cycles of R-CHOP with markedly improved visual acuity and no evidence of recurrence.
Biopsy fixation details: Biopsy of iris, fixed in buffered formalin.
Frozen tissue available: no
Details of microscopic findings: Infiltration of the iris by large cells with open chromatin, frequently multiple peripheral nucleoli and high mitotic rate. Few admixed small cells and pigmented ciliary cells.
Immunophenotype: Positive: CD20, MUM1, BCL2, BCL6 (weak, heterogeneous), MYC (het.) **Negative:** CD5, CD3, CD10, CD23, LEF1, EBERs
Cytogenetics: not available
Molecular studies: Detection of MYD88 L265P mutation by allele-specific PCR. Panel sequencing is pending. A comparative analysis with the CLL could not be performed.
Proposed diagnosis: Primary iridal diffuse large B-cell lymphoma, non-germinal center type, MYD88 L265P mutated
Interesting feature(s) of submitted case: Primary intraocular lymphoma is rare and primarily manifests as DLBCL of retina and vitreous body, (primary vitreoretinal lymphoma (PVRL)), which is considered a subtype of PCNSL. PVRL and PCNSL are usually of non-germinal center type, as is our case. Primary iridal lymphoma is extremely rare, most cases are of DLBCL type. PVRL and primary iridal DLBCL need to be distinguished from primary chorioidal lymphoma, which is usually an extranodal marginal zone B-cell lymphoma with indolent behaviour.
In our patient with CLL, Richter transformation might be considered. However, she shows stable CLL, and MYD88 L265P is rare in CLL (3-4%) and occurs mainly in younger patients with good prognosis, but is common (60-80%) in PCNSL and PVRL. The DLBCL phenotype is more consistent with a secondary tumor. Of note, 15-20% of DLBCL in CLL patients are clonally unrelated and show a better prognosis.
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Breast implant-associated anaplastic large cell lymphoma with breast parenchymal involvement and recurrence post-mastectomy

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Case description: 70-year old woman with history of bilateral breast augmentation with textured silicone implants in 1994. In November 2015, she developed a painful right breast mass with possible right implant leak and underwent bilateral implant removal. “Atypical cells” associated with the removed implants were noted at an outside hospital, which was not further characterized. In October 2016, she opted to undergo prophylactic bilateral mastectomy in view of her strong family history of breast cancer. Her left breast mastectomy showed a 0.4 mm focus of ductal carcinoma in situ and the right breast was initially noted to have fibrocystic changes. The patient then underwent bilateral breast reconstruction with placement of subcutaneous gel implants. In July 2017, she noticed swelling of her right breast and was referred to Stanford Hospital. A peri-implant effusion was aspirated and the cytologic features were suspicious for breast implant-associated anaplastic large cell lymphoma. Imaging showed no other sites of disease. Bilateral implant removal and capsulectomy were performed and a breast implant-associated ALCL was confirmed. The 2016 right mastectomy was requested from the outside hospital and an ALK-negative ALCL was detected, presumably related to the previously removed 1994 breast implant. Because of parenchymal involvement, the patient was given Brentuximab vedotin.

Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Right breast mastectomy (2016): Two small nodules with central necrotic material palisaded by large pleomorphic lymphoma cells, which also involve adjacent breast ductules (PowerPoint images).
Right capsulectomy (2017): Large pleomorphic cells lining breast implant capsule (Power Point images and glass slides submitted).

Immunophenotype: Positive for CD30, CD43, CD4, CD7, Ki67
Negative for ALK1, CD3, CD8, CD20, PAX5, CKMIX, MOC31, Calretinin
Cytogenetics: FISH negative for ALK and DUSP22/IRF4.
Molecular studies: MyRisk hereditary cancer genetic test showed no clinically significant mutations.
Proposed diagnosis: Breast implant-associated anaplastic large cell lymphoma with breast parenchymal involvement and recurrence post-mastectomy.

Interesting feature(s) of submitted case:

1. Time interval for development of breast implant-associated ALCL suggests that the lymphoma was likely related to the 1994 breast implants.
2. Lymphoma detected in the mastectomy specimen after prior removal of breast implants made assessment of the relationship of the lymphoma to the implant capsule difficult.
3. In the 2017 capsulectomy, it was not possible to assess whether there was parenchymal involvement due to the lack of surrounding breast tissue due to the prior mastectomy.
4. Involvement of breast parenchyma by lymphoma and the potential for more aggressive behavior necessitated Brentuximab therapy.
5. This case raises the following questions: Is there an increased propensity for development of breast implant-associated ALCL in this patient due to an altered host immune microenvironment or genetic predisposition? Did the original ALCL persist despite bilateral implant removal and bilateral mastectomy?

EAHP18-LYWS-436

Primary cutaneous peripheral T-cell lymphoma associated with chronic inflammation in a surgical mesh implant

Luis Veloza[*1], Adriana García[2], Ruth Orellana[3], Olga Balague[4], Elias Campo[2]
[1]Pathology, University of Barcelona, [2]Pathology, Hospital Clinic, [3]Parc Tauli, [4]Hospital Clinic, Barcelona, Spain

Case description: 64 year-old woman who was treated with a surgical mesh for umbilical hernia in 2012. In 2016 she presented a subcutaneous nodule in the region of the surgical mesh which was diagnosed as a granulomatous lymphohistiocytic inflammatory process without morphological and immunophenotypical criteria of malignancy. Four days after the surgical procedure she presented a surgical site infection which was managed with antibiotics. In 2017 multiple erythematous and indurated subcutaneous nodules appeared in the same location. No significant lymphadenopathies or lesions in other locations were detected by computed tomography scans. No underlying immunodeficiency was reported.
Biopsy fixation details: The skin biopsies were fixed in 10% neutral buffered formalin.
Frozen tissue available: No frozen tissue available.
Details of microscopic findings: The skin biopsies of 2017 showed a dense and diffuse dermic lymphohistiocytic infiltrate which extended into underlying subcutaneous fibroadipose tissue. Atypical large cells with irregular nuclear contours and prominent nucleoli were also identified. Non-caseating granulomas were observed. Epidermotrophism and angiodestruction were not presented. Scattered mitosis were also seen.
Immunophenotype: Immunohistochemistry studies in the skin biopsy of 2017 showed that the atypical cells were uniformly positive for CD3, partially positive for CD4 while CD5, CD2 and CD7 were significantly lost. GATA3, PD1, TCRβF1 and cytotoxic granules (TIA and granzyme B) were positive in some atypical cells, whereas CD8, CD56, CD30, ALK, TCRγ, TCRδ and T-bet were clearly negative. EBV in situ hybridization (EBER) was negative with adequate positive control.
Cytogenetics: Not performed.
Molecular studies: TCR gamma and beta chain gene rearrangement studies detected a clonal peak in the skin biopsy of 2017. Subsequently, TCR gene rearrangement studies were performed in the biopsy of 2016 and intriguingly, we detected the same clonal peak of the skin biopsy of 2017.
Proposed diagnosis: Primary cutaneous peripheral T-cell lymphoma, NOS, associated with chronic inflammation in a surgical mesh implant
Interesting feature(s) of submitted case: This is an unusual case of primary cutaneous T-cell lymphoma, in which the diagnosis of other distinct entities such as primary cutaneous CD30+ lymphoproliferative disorder, primary cutaneous gamma/delta T-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type and granulomatous mycosis fungoides were excluded based on clinical, morphological and immunophenotypical findings.
It is peculiar the indolent clinical course without any specific treatment and the association with chronic inflammation in the setting of a surgical mesh implant in a non-immunosuppressed patient. Therefore, this case may represent a T-cell lymphoproliferative disorder associated with chronic inflammation and may expand the clinical and pathological spectrum of lymphoid neoplasms related to chronic inflammation.

EAHP18-LYWS-461

Fibrin-associated large B-cell lymphoma presenting as adrenal mass

Yan Xie[*1], Paul W. Stout [2], Eric D. Hsi[1]
[1]Laboratory Medicine, Cleveland Clinic Foundation, Cleveland, [2]Pathology, Arkansas Pathology Associates, Arkansas, United States

Case description: The patient is a 70 year old male with a past medical history of renal cell carcinoma of the left kidney and prostatic adenocarcinoma. He presented with a left adrenal mass, which was first notice by CT scan after the nephrectomy. This was observed and remained stable for approximately 5 years but slowly enlarged over the last several months. The mass (15x12.5x7.5 cm) appeared to be attached to the left adrenal gland and was excised together with the adrenal gland.
Biopsy fixation details: 10% neutral buffered formalin.
Frozen tissue available: Not Available
Details of microscopic findings: Histologic sections demonstrate a pseudocyst consisting of a rim of fibrous tissue with chronic inflammation and benign-appearing adrenal gland tissue. The pseudocyst contains hemorrhage and fibrin with a layer of atypical intermediate to large lymphoid cells with open chromatin. Many of the cells contain visible nucleoli. Apoptotic cells were also present. The atypical cells appear confined to the interior of the pseudocyst.
Immunophenotype: The atypical cells expressed CD20, MUM-1, PAX5 (weak subset), BCL-2 (90%), c-MYC (40%), PD-L1, and Indoleamine-pyrrole 2,3-dioxygenase (IDO1). The Ki-67 proliferative index is high (80-90%). The cells were negative for CD3, CD10, CD30, BCL6, Cyclin D1, and TDT. They were also negative for the immune check point-related molecules PD-1, CD200, B7-H3, Lag3, Tim3, and VISTA (5% cut off for all immune check point molecules).
Cytogenetics: Not performed
Molecular studies: EBER in situ hybridization is positive.
Proposed diagnosis: Fibrin-associated diffuse large B-cell lymphoma (FA-DLBCL).
Interesting feature(s) of submitted case: These unusual lymphomas present in a restricted anatomic space and are associated with pseudocysts, cardiac myxoma, prosthetic cardiac valves, chronic subdural hematomas, and hematomas or thrombi associated with sites of prior vascular surgery. They occur in a background of abundant fibrin, are typically associated with EBV-infection (latency III), and have an indolent clinical course and favorable clinical outcome. They have large cell morphology, non-germinal center B-cell phenotype, high Ki67 fraction, often express CD30, and also demonstrate PD-L1 expression. They are reported to have low to moderate MYC and TP53 expression.
Transformation and immortalization by EBV might contribute to the pathogenesis of FA-DLBCLs. In addition, immune evasion may play a role. We evaluated this case for a set of immune-checkpoint molecules (receptors PD1, LAG3, TIM3 and VISTA; ligands PD-L1, B7-H3, CD200, VISTA; and IDO1). The lymphoma cells expressed high levels of PD-L1 and IDO1 but were negative for PD1, CD200, LAG3, TIM3, VISTA and B7-H3. Local T-cells in the capsule expressed PD1, IDO1, TIM3, and VISTA, but lacked PD-L1, CD200, LAG3, and B7-H3. These findings suggested that checkpoint molecules might be important in lymphomagenesis. The location within an "immune-privileged" site may also protect the cells from immune surveillance, but also might prevent dissemination.
Despite aggressive histopathologic features (non-germinal center and "double expresser", high Ki67), these lymphomas have an indolent clinical course and favorable clinical outcome. Surgical excision can be curative. The patient received no further therapy and has no evidence of disease at 13 months.

EAHP18-LYWS-461

Fibrin-associated large B-cell lymphoma presenting as adrenal mass

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[1]Laboratory Medicine, Cleveland Clinic Foundation, Cleveland, [2]Pathology, Arkansas Pathology Associates, Arkansas, United States

Case description: The patient is a 70 year old male with a past medical history of renal cell carcinoma of the left kidney and prostatic adenocarcinoma. He presented with a left adrenal mass, which was first notice by CT scan after the nephrectomy. This was observed and remained stable for approximately 5 years but slowly enlarged over the last several months. The mass (15x12.5x7.5 cm) appeared to be attached to the left adrenal gland and was excised together with the adrenal gland.
Biopsy fixation details: 10% neutral buffered formalin.
Frozen tissue available: Not Available
Details of microscopic findings: Histologic sections demonstrate a pseudocyst consisting of a rim of fibrous tissue with chronic inflammation and benign-appearing adrenal gland tissue. The pseudocyst contains hemorrhage and fibrin with a layer of atypical intermediate to large lymphoid cells with open chromatin. Many of the cells contain visible nucleoli. Apoptotic cells were also present. The atypical cells appear confined to the interior of the pseudocyst.
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Cytogenetics: Not performed
Molecular studies: EBER in situ hybridization is positive.
Proposed diagnosis: Fibrin-associated diffuse large B-cell lymphoma (FA-DLBCL).
Interesting feature(s) of submitted case: These unusual lymphomas present in a restricted anatomic space and are associated with pseudocysts, cardiac myxoma, prosthetic cardiac valves, chronic subdural hematomas, and hematomas or thrombi associated with sites of prior vascular surgery. They occur in a background of abundant fibrin, are typically associated with EBV-infection (latency III), and have an indolent clinical course and favorable clinical outcome. They have large cell morphology, non-germinal center B-cell phenotype, high Ki67 fraction, often express CD30, and also demonstrate PD-L1 expression. They are reported to have low to moderate MYC and TP53 expression.
Transformation and immortalization by EBV might contribute to the pathogenesis of FA-DLBCLs. In addition, immune evasion may play a role. We evaluated this case for a set of immune-checkpoint molecules (receptors PD1, LAG3, TIM3 and VISTA; ligands PD-L1, B7-H3, CD200, VISTA; and IDO1). The lymphoma cells expressed high levels of PD-L1 and IDO1 but were negative for PD1, CD200, LAG3, TIM3, VISTA and B7-H3. Local T-cells in the capsule expressed PD1, IDO1, TIM3, and VISTA, but lacked PD-L1, CD200, LAG3, and B7-H3. These findings suggested that checkpoint molecules might be important in lymphomagenesis. The location within an "immune-privileged" site may also protect the cells from immune surveillance, but also might prevent dissemination.
Despite aggressive histopathologic features (non-germinal center and "double expresser", high Ki67), these lymphomas have an indolent clinical course and favorable clinical outcome. Surgical excision can be curative. The patient received no further therapy and has no evidence of disease at 13 months.

EAHP18-LYWS-507

Primary Effusion Lymphoma

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Case description: 80 year old male. Presented to the emergency department with acute sudden central chest pain. Progressive increase in shortness of breath and fatigue over last few weeks. Associated orthopnoea. Occasional productive cough. No other symptoms on systems enquiry. No previous episodes of chest pain. No fevers, night sweats, weight loss. BP 102/86, HR 73, RR 21, Afebrile. HS dual nil added. Chest; dull right base. No hepatosplenomegaly or adenopathy. Full blood count normal, with normal differential. Blood film examination is normal. CXR: increased cardiac silhouette, elevated R hemidiaphragm +/- right pleural effusion. Upper abdominal US Scan: moderate **ASCITES**, non-specific gall bladder wall thickening, bilateral pleural effusions. Significant deterioration on days 3, noted to have symptoms of cardiac shock. ECHO showed **CARDIAC TAMPONADE**. Urgent pericardiocentesis: drained ~700mL fluid. CT chest/abdo/pelvis done: NO enlarged lymph nodes, masses, or hepatosplenomegaly. Cardiac fluid morphology and flowcytometry consistant with primary effusion lymphoma. Patient was HIV & HHV-8 negative but EBV positive.
Biopsy fixation details: Fixation – Formalin for 24 hrs Decalcification – 10% Formic Acid for 6 hrs
Frozen tissue available: No
Details of microscopic findings: The cell block contains large numbers of lymphoid cells including the population of medium to large atypical lymphocytes. There are clumped macrophages admixed with fibrin. A strip of mesothelial cells shows reactive atypia. The appearance is suspicious for lymphoma. On immunostaining there are only scant and small T-lymphocytes highlighted with CD3 and CD5. The majority of lymphocytes are CD79a and CD20 positive and these are medium to large in size. This population of B-lymphocytes is CD10 negative and CD5 negative, and shows no-to-faint nuclear staining for MUM1, interpreted as negative. The B-lymphocyte population is negative for Bcl-6 and positive for Bcl-2. Kappa and Lambda are not expressed. Cyclin D1 is negative. EBV-ish is negative. A Ki67 is approximately 35% in the monotonous population. A CD30 highlights scattered single large cells with moderately abundant cytoplasm and a large round to oval nucleus, one cell binucleate. The staining pattern supports the H and E impression of a lymphoma, which appears to have a post germinal centre B-lymphocyte phenotype. DIAGNOSIS: PERICARDIAL FLUID: IN KEEPING WITH A B-CELL LYMPHOMA.
Immunophenotype: Flow cytometry on the large lymphoid cells shows a predominance of B-cells with no light chain expression. The cells are positive for the pan B-cell markers and are negative for CD10 and CD5. Ki-67 is moderately raised at 32%. The results are consistent with CD10 negative Large B-cell lymphoma. Primary effusion lymphoma is a possibility"
Cytogenetics: FISH Studies Showed:

MYC (8q24) - Rearranged, BCL6 (3q27) - Not rearranged, IGH-BCL2 [t(14;18)] - Absent, additional BCL2 and IGH signal
Molecular studies: Not done
Proposed diagnosis: Primary Effusion Lymphoma (PEL).
Interesting feature(s) of submitted case: PEL in a patient who is HIV & HHV-8 negative.

EAHP18-LYWS-514

Stab wound to the chest: culprit for an anaplastic large cell lymphoma, ALK-negative in a young man?

Axelle CANARD[*1,2], Ramy RAHME[3], Pascale CERVERA[1,2], Malek AOUDJHANE[4], Alexander VALENT[5], Jean-François FLEJOU[1,2], Fabrizia FAVALE[1,4], Bettina FABIANI[2]
[1]Sorbonne University, [2]PATHOLOGY, HUEP APHP, [3]HEMATOLOGY, HOPITAL SAINT LOUIS , [4]HEMATOLOGY, HUEP APHP, PARIS, [5]MOLECULAR BIOLOGY, INSTITUT GUSTAVE ROUSSY , VILLEJUIF, France

Case description: A 20-year-old man without any medical history, HIV negative, presented in March 2017 to the emergency department with a chronic septic thoracic wound. One year ago, he was victim of a stab wound in the thorax region that he self-treated with basic local treatment without any specific product. For six months, he has had recurrent secondary local infections treated with antibiotics. The day he was admitted to hospital, his physical examination revealed no other abnormalities except from a suppurating skin lesion. He underwent surgical excision of the wound edges.
Biopsy fixation details: Buffered formalin fixation.
Frozen tissue available: No frozen material available.
Details of microscopic findings: The dermis of the wound edges was diffusely infiltrated by sheets of atypical large cells admixed with some small lymphocytes. Large cells had irregular nuclei with sometimes prominent nucleoli, hallmark cells were present. Epidermis pseudoepitheliomatous hyperplasia was seen.
Immunophenotype: The large cells were positive for CD45, CD30, EMA, MUM1, Perforin, CD2, CD5, CD4 and negative for ALK, CD3, CD43, CD7, CD8, CD20, PAX5, EBV (EBER).

Cytogenetics: Not done.
Molecular studies: No DUSP22 rearrangement was detected by FISH.
TCR was clonally rearranged.
Proposed diagnosis: Anaplastic large cell lymphoma, ALK-negative, occurring on the edges of a neglectous cutaneous stab wound.
Interesting feature(s) of submitted case: Besides ALK-positive and ALK-negative anaplastic large cell lymphoma, 2016 WHO classification recognizes as a new provisional entity, ALK-negative ALCL arising in association with breast implants (i-ACL).It is thought that chronic inflammatory stimulation may explain the development of such lymphomas.
Our case occurring after chronic inflammation lasting over one year and favoured by subsequent infections of a neglitected cutaneous wound, could have similarities to the infiltrative form of i-ALCL. Immunologic response to this chronic and subacute cutaneous inflammation might have trigger ALCL proliferation.
The patient was lost of follow-up until October 2017 when he presented with a large axillary lymph node; needle biopsy showed the same morphology corresponding to the ALCL ALK-, previously diagnosed in March 2017. PET SCAN showed a localized disease and the patient started ACVBP regimen.

EAHP18-LYWS-533

BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA WITH PD-L1 EXPRESSION

Luis Colomo[*1], Natalia Papaleo[1]
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Case description: 49 years old female diagnosed of breast carcinoma in 2003 (pT2N2M0); the patient was treated with surgey, chemotherapy and radiotherapy, and a breast prosthesis was implanted. The patient remained in complete remission until November 2014, when she presented repeated seromas and an increase of the size of the breast.
The PET study breast involvement with no other active sites, and the cytological examination of the cells of the aspirated effusion fluid suggested lymphoma. Excision of the capsule and breast implant were performed.
Biopsy fixation details: Formalin fixed paraffin-embedded biopsy
Frozen tissue available: No
Details of microscopic findings: The tumor cells were attached to the capsule but did not invade it (no masses were identified); many cells were embedded in the serofibrinoid material of the seroma. On morphological grounds, the cells were large and pleomorphic, and formed small clusters admixed with histiocytes and few lymphocytes.
Immunophenotype: The tumor cells expressed CD30, CD4 (focally), CD7 (focally), and TIA-1.
ALK1, CD2, CD3, CD5, CD8, CD56, beta-F1, CD20 and EBV (by HIS) were negative. Ki-67 was high (80-90%).
MYC protein, p53 and GATA3 were expressed in 25 to 50% of cells approximately.
PD-L1 (clones SP263 and 142) was strongly expressed in most tumor cells.
Cytogenetics: MYC split FISH: gains in 25% of cells (3-5 copies)
P53 FISH: polysomy (3-5 copies TP53/CEN17)
PD-L1 FISH: polysomy (3-5 copies PDL1/CEN9)
Molecular studies: Clonal TCR gamma and beta
Proposed diagnosis: Breast implant-associated anaplastic large cell lymphoma.
Interesting feature(s) of submitted case: We suggested the diagnosis of BI-associated ALCL. The disease presented as seromas after 11 years of breast implant. The patient remains alive without evidence of disease 36 months after the diagnosis of lymphoma, without receiving additional treatments.
The tumor cells expressed strong PD-L1 and cytogenetics suggested polyploid tumor cells without structural alterations in PD-L1 gene.

EAHP18-LYWS-539

Diffuse large B-Cell lymphoma associated with chronic inflammation or fibrin-associated EBV-positive large B-Cell lymphoma, involving an epidermoid cyst in the central nervous system.

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[1]pathology, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Spain

Case description: The patient is a forty-year old male with a history of an epidermoid cyst situated in the central nervous system dating back over twelve years. Despite various surgical procedures, there have been multiple relapses. The last MRI has revealed a solid lesion/tumour around the cyst. It was decided to perform a biopsy on the tumour.
Biopsy fixation details: Buffered 10% formalin.

Frozen tissue available: No
Details of microscopic findings: Histologic examination disclosed the cystic portion to be an epidermoid cyst, whereas the solid tumour showed a proliferation of large atypical lymphoid cells with prominent apoptosis and associated with chronic inflammation.
Immunophenotype: The cells were positive for EBV by EBV-encoded small RNA in situ hybridization and positive for CD20, CD79a, PAX5, CD30, CD138, MUM1 and C-MYC. Light chains showed kappa light restriction. Ki67 proliferation index was high (>90%). LMP-1 and BZLF-1 were negative. EBNA2 failed. Aberrant expression of T-cell markers was seen. CD3 and CD7 were positive. CD2, CD5, CD4 and CD8 were negative. P53 negative.
Cytogenetics: MYC FISH: no rearrangement.
Molecular studies: A clonal T-cell rearrangement beta was identified by PCR. Immunoglobulin gene rearrangement (IgH FRIII) was polyclonal.
Proposed diagnosis: Diffuse large B-Cell lymphoma associated with chronic inflammation.
Interesting feature(s) of submitted case: We report a case of EBV+ large B-cell lymphoma occurring in an epidermoid cyst in CNS. The interesting feature of the case is that it shares characteristics with the fibrin-associated EBV-positive large B-cell lymphomas (large cells, prominent apoptotic activity, a nongerminal center phenotype and high KI67 proliferative index), but in our case there is a history of long standing chronic inflammation, a mass forming lesion and bad prognosis that it favors the diagnosis of diffuse large B-cell lymphoma associated with chronic inflammation.

EAHP18-LYWS-551

Fibrin-associated EBV+ large B-cell lymphoma occurring in an adrenal pseudocyst

Alina Nicolae[*1], Clarisse Cazelles[2], Cecile Charpy[2], Maya Nourieh[2], Christiane Copie-Bergman[2], Nicola De'Angelis[3]
[1]Hôpital Henri Mondor, Créteil, France, [2]Pathology, [3]Surgery, Hôpital Henri Mondor, Créteil, France

Case description: A 48 yo man was admitted for acute right flank abdominal pain. The WBC, LDH, liver, kidney and endocrinological tests were unremarkable. Serology for Echinococcus, HIV, VHB and VHC were negative. EBV viral load was undetectable. Abdominal ultrasound and MRI identified a right 10 cm adrenal cystic lesion, compatible with a hydatiform cyst. A right adrenelectomie was performed. A diagnosis of DLBCL-CI was made, the workup disclosed stage IE disease and 6xR-CHOP were given. With 8 months of follow-up, the patient is in complete remission.
Biopsy fixation details: 10% neutral buffer formalin.
Frozen tissue available: No
Details of microscopic findings: Gross examination revealed a cystic lesion (10 cm diameter). The cut surface showed a multiloculare appearance, with thin walls and gelatinous content. No gross evidence of tumor was identified. Sections of the adrenal lesion revealed a hyalinized fibrous wall with no luminal lining. Entrapped adrenal cortical cells, a mild lymphocytic infiltrate and numerous dilated capillaries were present between the collagenous bands. The lumen of the pseudocyst was filled with fibrin, blood, necrotic debris, degenerative calcification, and scattered hemosiderin-laden macrophages. Nests of atypical medium to large lymphocytes, with round or polylobalted nuclei, dense chromatin, inconspicuous nucleoli and scarce cytoplasm were seen. The neoplastic cells either floated in the fibrinous material or lined the inner surface of the fibrous wall, without infiltrating it.
Immunophenotype: The neoplastic cells were positive for CD22, PAX5, MUM1, Bcl-2 and focally expressed CD79a, CD30 and CD138. They showed an EBV latency type III (EBER+, LMP1+ and EBNA2+). The atypical lymphocytes were negative for CD20, CD10, Bcl-6, CD3, CD5, c-Myc, p53, ALK1 and HHV8/LANA. Ki-67 showed a high proliferation fraction (90%).
Cytogenetics: Interphase FISH study: lack of rearrangements involving chromosomal gene loci 8q24/MYC;, 18q21/BCL2, and 3q27/BCL6
Molecular studies: A PCR study for IG gene rearrangement showed a monoclonal rearrangement pattern in FRI, FRII and FRIII-IGH with polyclonal pattern for the Vκ. An NGS study is pending.
Proposed diagnosis: Fibrin-associated EBV+ large B-cell lymphoma occurring in an adrenal pseudocyst
Interesting feature(s) of submitted case: Our case illustrates a rare example of fibrin-associated EBV+ large B cell lymphoma occurring within an adrenal pseudocyst. Only two other similar cases have been described to date in this location. The recent WHO classification includes these lesions under the spectrum of large B cell lymphoma associated with chronic inflammation (DLBCL-CI), which was our initial diagnosis. However, our case as those recently reported by Boyer et al. emphasized significant clinicopathological differences between fibrin-associated EBV+ large B cell lymphoma and DLBCL-CI, which might warrant their separate classification. Although our patient showed microscopic lesions restricted to the adrenal pseudocyst, he received 6 cycles of chemotherapy. In the literature, similar cases of fibrin-associated EBV+ large B cell lymphoma associated with pseudocysts behave indolently and a conservative management with surgery alone is proposed. The pathogenesis of this lymphoproliferation is not completely understood. Our case showed an EBV latency type III in the absence of rearrangements of BCL2, MYC and BCL6 genes or significant p53 expression. It might be that EBV infection in the context of local immunosuppression might suffice to trigger the lymphoid expansion and transformation and might supplant the need for cytogenetic or molecular abnormalities.

LYMPHOMA WORKSHOP SESSION 3

Gastrointestinal lymphoproliferative disorders

(T-cell)

Chairs: M. Calaminici, S. Montes-Moreno

EAHP18-LYWS-421

Indolent CD4+ T-cell lymphoproliferative disorder of the small bowel

Gloria Madrid-Valero[*1,2], Horacio Decanini-Arcaute[2], Leticia Quintanilla-Martinez[3]
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Case description: A 56-year-old man presents with a 4 year history of intermittent bouts of diarrhea and weight loss. As part of his work up in a new institution a CT scan was performed, revealing thickening of the initial segment of the jejunum wall and mesenteric lymphadenopathies measuring up to 2.2 cm. A lymph node and a 2 cm long, full thickness bowel biopsy were resected. Six months after the biopsy the patient continues with diarrhea without any treatment.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: The architecture of the small bowel demonstrated slight flattening of the intestinal villi with no ulceration. In the lamina propria there was a dense and diffuse lymphoid infiltrate that for the most part remained in the mucosa with minimal spillover to the submucosa and displaced rather than destroyed the glandular structures. Only mild increase in intraepithelial lymphocytes was observed but without histological changes of celiac disease. This infiltrate was composed primarily of small lymphocytes with mature chromatin and scant clear cytoplasm, abundant plasma cells without atypia were observed, mainly in the intestinal villi and the submucosa. The lymph node showed a partially preserved architecture with open sinuses and secondary follicular structures present, but there was expansion of the medullary chords and slight paracortical infiltrate with prominent plasma cells.
Immunophenotype: The lymphoid infiltrate of the bowel wall was mainly composed of CD3+, CD4+, CD8-, CD56-, with aberrant CD20 expression, and a small subset of CD8-CD4-CD3+ cells was observed. The proliferation rate was less than 5% as demonstrated with the MiB1 stain. EBER ISH was negative. The plasma cell infiltrate was positive for CD138 and polytypic as shown by ISH for kappa and lambda light chains. A subtle infiltrate with the same immunophenotype was observed in the lymph node indicating lymph node infiltration.
Cytogenetics: No
Molecular studies: PCR analysis for TCR genes rearrangement of the CDR3-region of the TCR gamma chain gene demonstrated the same monoclonal peak in the small bowel and the lymph node.
Proposed diagnosis: Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract with prominent plasma cell infiltrate and regional lymph node involvement.
Interesting feature(s) of submitted case: 1)Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract is a rare entity newly described in the revised 2016 WHO classification. Although this type of disorder usually is CD8+, some cases (such as this one) have been reported as CD4+.
2)The T-cells in this case have aberrant CD20 expression, which has been reported before in T-cell lymphomas, as well as normal circulating T-cells. In this case, this feature was helpful to recognize the presence of the abnormal T-cell population in the lymph node.
3)The lymphoid infiltrate is not usually associated with admixed inflammatory cell, with the exception of epitheloid granulomas. However, in this case there was a marked plasma cell infiltrate, which was proved to be polytypic and has not been previously described in this entity.
4)Most of the cases described with this diagnosis are confined to the GI tract; however, a small group of patients present with regional lymphadenopathy, usually mesenteric, which have not been morphologically analyzed. In this case, the phenotype and molecular analyses performed in the lymph node confirmed the presence of monoclonal T-cell with the same characteristics as the ones observed in the small bowel, indicating that the intestinal infiltrate can extend to the regional lymph nodes.

EAHP18-LYWS-252

Novel somatic JAK3 and AXL mutations in NK-cell enteropathy: genetic evidence of a neoplastic process

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Case description: 76-year-old female presented with nonspecific dyspepsia for a few years. An upper GI endoscopic examination performed 2 years ago showed multiple superficial ulcers in duodenal and gastric mucosa. A biopsy was performed and an NK-cell proliferation was noted. Recently, a repeated upper GI endoscopic examination showed similar findings and another biopsy was taken. The patient had no lymphadenopathy or B-symptoms and PET scan showed no avid uptake.
Biopsy fixation details: 10% neutral Formalin fixed
Frozen tissue available: not done
Details of microscopic findings: Fragments of gastric mucosa with a dense lymphoid infiltrate in the lamina propria. The lymphoid cells are small in size and only show mild atypia. There is no epitheliotropism.
Immunophenotype: Immunohistochemical stains show atypical lymphoid cells are positive for CD2, CD3 (cytoplasmic), CD56 (strong), TIA1 and granzyme B, while being negative for CD5, CD4, CD8, TCRbeta, TCRdelta, CD25, CD30, PD-1 and EBER. Ki-67 proliferation index is 40%. Kappa or Lambda light chain immunostains show polyclonal plasmacytosis. Immunohistochemical stain for H. Pylori is negative.
Cytogenetics: not done
Molecular studies: No clonal TCRgamma gene rearrangements detected
Mutational analysis by MSK IMPACT (400 genes): POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS IN THE INVESTIGATIONAL PANEL (WITH MATCHED NORMAL CONTROL NAIL DNA):
1. AXL (NM_021913) exon18 p.L721I (c.2161C>A), VAF 7%
2. JAK3 (NM_000215) exon12 p.K563_C565del (c.1688_1696delAGAACTGCA), VAF 8%
Proposed diagnosis: NK-cell enteropathy
Interesting feature(s) of submitted case: NK-cell enteropathy is a rare type of NK-cell proliferation occurring in GI tract, usually presents with multiple superficial ulcers that can be persistent/recurrent, refractory to treatment and have indolent clinical course (1-2). While the nature of this proliferation as neoplastic versus reactive is uncertain, it is prudent not to misdiagnose this entity as aggressive NK or T-cell lymphoma that are often fatal. Key features to differentiate from the latters are: 1. Patients have no B-symptoms or lymphadenopathy; 2. The infiltrate is superficial; 3. The cells have no significant atypia; 4. The cells have NK phenotype; 5. EBV is negative.
To our knowledge, this is the first report of mutations on NK-cell enteropathy, supporting it as a neoplastic rather than reactive process. JAK3 mutations are often seen in NK/T-cell lymphoproliferative disorder/lymphoma. AXL is a member of TAM receptor family that has been reported to be indispensible for NK cell development and function in mouse model (3-4). Sequencing studies on additional cases and functional validation of this AXL mutation are ongoing in our laboratory. The results will be made available at the meeting.
Reference:
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3. Caraux A, et al. Natural killer cell differentiation driven by Tyro3 receptor tyrosine kinases. Nat Immunol. 2006 Jul;7(7):747-54. Epub 2006 Jun 4.
4. Paolino M, et al.The E3 ligase Cbl-b and TAM receptors regulate cancer metastasis via natural killer cells. Nature. 2014 Mar 27;507(7493):508-12. doi: 10.1038/nature12998. Epub 2014 Feb 19.

EAHP18-LYWS-276

Evolving enteropathy-associated T-cell lymphoma

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Case description: A 45 year old female presented in July 2017 with intermittent abdominal pain, diarrhea, nausea and vomiting at which time she was diagnosed with celiac disease. She did not readily respond to a gluten free diet. She was admitted in Nov 2017 for a second evaluation. Review of systems at this time revealed a 14 kg weight loss over the prior 6 weeks.
Tissue transglutaminase antibody levels were reportedly mildly elevated (16.2 U/mL).
Upper gastrointestinal endoscopy showed flattened and diminished mucosal folds, mild scalloping, marked erythema and a few superficial ulcers in the duodenum. Colonoscopy was unremarkable. CT scan of the abdomen revealed focal thickening of the small intestinal wall. Abdominal MRI showed prominent but non-specific changes in the mesenteric lymph nodes.
Biopsy fixation details: Specimen was fixed in 10% neutral buffered formalin.
Frozen tissue available: N/A
Details of microscopic findings: Sections of the duodenal mucosa show significant villous atrophy, intraepithelial lymphocytosis and expansion of the lamina propria by a polymorphous infiltrate consisting of plasma cells, eosinophils, histiocytes and small lymphocytes. No necrosis is seen.
Scattered lymphocytes appear atypical with medium to large-sized nuclei, irregular nuclear contours, hyperchromatic chromatin, and scant to moderate amount of cytoplasm. They are mostly localized within the epithelium, with possible rare forms seen within the lamina propria.
Immunophenotype: The pleomorphic medium to large-sized intraepithelial lymphocytes are positive for CD3, CD7 (strong), CD30, CD103, granzyme B (partial), and TIA1 (partial, weak). These cells, which are only occasionally present within the lamina propria, are negative for CD2, CD4, CD5, CD8, CD20, CD56, ALK, T-cell receptor (TCR) beta F1 and TCR delta.
Most of the small lymphocytes in the lamina propria are reactive to CD2, CD3, CD5, and CD7 (partial, weak) and are alpha-beta (TCR beta F1-positive) T-cells that are divided into CD4-positive and CD8-positive subsets. Few CD20-positive B-cells are seen.
In situ hybridization was performed using probes that recognize Epstein-Barr virus encoded RNA (EBER). The lymphocytes are negative for EBV.
Cytogenetics: N/A
Molecular studies: FISH analysis for DUSP22(IRF4) performed on parrafin-embedded sections showed no rearrangement of the DUSP22(IRF4) gene region.
T-cell receptor gene rearrangement analysis by a PCR-based assay was performed on extracted DNA using primers that bind the gamma and beta chain genes on paraffin-embedded sections. It was interpreted as equivocal with suboptimal amplification of T-cell receptor target DNA.
Proposed diagnosis: Atypical intraepithelial cytotoxic T-cell infiltrate with features suggestive of evolving enteropathy-associated T-cell lymphoma (EATL).
Interesting feature(s) of submitted case: The presence of pleomorphic medium to large-sized intraepithelial cells (IELs) that have an aberrant T-cell phenotype, including CD30 expression, suggests this patient's celiac disease is evolving into an EATL - despite the absence of a small intestinal mass and only slight infiltration of the abnormal T-cells into the lamina propria. CD30 expression on intraepithelial T-cells in patients with refractory celiac disease has been associated with transformation to EATL [1].
This may represent a Type II refractory celiac disease with possible early transformation to EATL. An important question to answer in this case and others like it is: does CD30 expression by phenotypically aberrant IELs that do no form a mass or homogeneous aggregates in the lamina propria truly indicate a diagnosis of EATL?
[1]Farstad IN et al. Gut. 2002 Sep;51(3):372-8.

EAHP18-LYWS-281

Enteropathy-associated T-cell lymphoma with DUSP22/IRF4 gene rearrangement presenting as large jejunal mass

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Case description: A 58 year old male, diagnosed with celiac disease 5 years earlier by duodenal biopsy, presented in January 2014 with severe abdominal pain. A mid-jejunal segmental resection contained a 7.5 x 6.8 x 5.5 cm annular mass. Following diagnosis, CHOP chemotherapy produced a 3 year remission. The patient developed small bowel obstruction in Sepember 2017 due to recurrent tumor. He received 3 cycles of ICE salvage chemotherapy but died of progressive disease on January 1, 2018.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: Yes
Details of microscopic findings: Pleomorphic intermediate-sized to large lymphocytes were concentrated in the submucosa and muscularis propria, extended into the mesentery and involved 5 of 12 mesenteric lymph nodes. Portions of the intact mucosa contained pleomorphic small lymphocytes that were concentrated in the lamina propria and showed little infiltration beyond the muscularis mucosa. There were scattered eosinophils and histiocytes throughout the lymphoma. Adjacent uninvolved mucosa showed mild villous blunting and an increased number of intraepithelial lymphocytes (IELs).
Immunophenotype: Intermediate-sized to large cells: CD2+, CD30 (strong)+, CD43+, CD45+, clusterin+, granzymeB+, MUM1+, PAX5 (partial)+ and TIA1+; CD3-, CD4-, CD5-, CD7-, CD8-, CD19-, CD20-, CD56-, CD79a-, ALK-, EMA-, TCR betaF1- and TCR delta-
Small cells: same as above except weak CD30+ and MUM1- and PAX5-
Cytogenetics: FISH: DUSP22/IRF4 rearrangement in 100% of interphase nuclei using break apart probes for 6p25.3 (DUSP22/IRF4)
No TP63 rearrangement detected using break apart probes for 3q28 (TP63) and dual fusion probes for 3q26.32 (TBL1XR1) and 3q28 (TP63)

Molecular studies: Clonal T-cell receptor (TCR) beta and gamma chain gene rearrangements detected and no immunoglobulin gene rearrangements identified using a PCR-based assay and BIOMED2 primers
Proposed diagnosis: Enteropathy-associated T-cell lymphoma (EATL) with DUSP22/IRF4 rearrangement
Interesting feature(s) of submitted case: A diagnosis of EATL, rather than ALK- anaplastic large cell lymphoma with DUSP22/IRF4 rearrangement, was supported strongly by review of the prior duodenal biopsy that showed features of celiac disease including a malabsorption pattern with partial and focal total villous blunting, crypt hyperplasia and intraepithelial lymphocytosis (50 to 70 lymphocytes per 100 epithelial cells). IELs were small; expressed CD2, CD3 and CD7; showed partial, weak CD30 staining; and lacked CD4, CD5, CD8, TCR betaF1 and TCR delta. The relationship to the subsequent jejunal lymphoma was supported by an identical clonal TCR gene rearrangement and by the presence of DUSP22/IRF4 rearrangement in 63% of nuclei. The latter finding, exceptional in EATL, also indicates that that genetic abnormality can be seen in some celiac disease precursor lesions. Furthermore, the biphasic pattern of small lymphocytes with weak CD30 in the mucosa and large lymphocytes with strong CD30 in the submucosa and muscularis propria of the EATL is analagous to cases of lymphomatoid papulosis with DUSP22 rearrangement in which small cerebriform lymphocytes with weak CD30 are in the epidermis and large lymphocytes with strong CD30 are in the dermis (Am J Surg Pathol 37:1173, 2013). It is unclear to what extent, if any, the DUSP22/IRF4 rearrangement influenced the patient's near 4 year survival as compared to the median 7 month survival for patients with EATL.

EAHP18-LYWS-311

Monomorphic epithelial intestinal T-cell lymphoma beyond the intestines

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Case description: Man born in 1975, originating from Macedonia, without previous medical history who underwent resection of a small bowel tumor in August 2016, diagnosed as MEITL. Staging procedures showed infiltration of the mesentery, and mild interstitial bone marrow infiltration. The patient received 5 courses of CHOP until November 2016. In December 2016, he presented with upper abdominal symptoms and duodenal and gastric biopsies showed mucosal infiltration by lymphoma. The patient then received another chemotherapy regimen consisting of asparaginase, gemcitabine, oxaliplatin and dexamethasone followed by BEAM intensification and autologous stem cell transplantation, but digestive symptoms recurred. Gastric biopsies were taken (submitted specimen, H1704815). His condition rapidly worsened and the patient died early April 2016. An autopsy was performed, showing massive multiorgan involvement by lymphoma (submitted sample, liver – A17-14).
Biopsy fixation details: Formalin and B+ fixation.
Frozen tissue available: From autopsy.
Details of microscopic findings: H1704815 (stomach biopsies):
Diffuse lymphomatous infiltrate of the gastric mucosa by medium-sized cells featuring epitheliotropism.

A1700054 (liver, autopsy):
Diffuse mass-like lymphoma infiltrate, with sinusoidal and epitheliotropic ("emperipoletic") dissemination in the hepatic lobules.

Immunophenotype: Intestinal lymphoma – 08/2016: CD2+, CD3+, CD4-, CD5-, CD7+, CD8+/-, CD56+/-, activated cytotoxic phenotype, 90% Ki67, TCR-gamma+, TCR-betaF1-, CD20-, CD79a-, CD103-/+, EBER-.
Stomach – 12/ 2016: CD20-, CD3+, CD4-, CD5-, CD30-, CD56+, TIA1+, CD8+, Ki67: 95%.
Stomach – 03/ 2017: CD3+, TIA1+, Ki67: 95%.
Liver – 04/2017: CD3+, immunophenotype not extensively repeated.
Cytogenetics: Not done.
Molecular studies: Molecular characterization performed on the initial intestinal tumor:
- Monoclonal rearrangement of TRG and TRB genes.
- FISH studies: monoallelic deletion of the SETD2 locus; small copy number gain of the MYC locus (FISH).
- Sequencing analysis for T-cell lymphoma panel: SETD2 mutations, c.6118C>T/T (p.Arg2040*) and c.1833G>T (p.Lys611Asn).

Proposed diagnosis: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).

Interesting feature(s) of submitted case: This case of MEITL was primarily refractory to therapy, and ended in diffuse gastrointestinal and multivisceral dissemination. Dissemination to the stomach showed markedly epitheliotropic features similar to what is characteristic in the intestinal mucosa for this entity. Besides the destructive mass-forming lesion in the liver, there was dissemination into the hepatic lobules in the form of sinusoidal involvement and emperipolesis into the hepatocytes. This remarkable image is yet undescribed. The sinusoidal dissemination observed in the liver (and also in the spleen) in this autopsy case is a feature that overlaps with what is typically observed in hepatosplenic T-cell lymphoma, which is another T-cell lymphoma of gamma-delta derivation. In other organs also infiltrated by lymphoma (lung, prostate, kidney), lymphoepithelial lesions were also observed.

EAHP18-LYWS-124

Indolent CD8(+) T-cell lymphoproliferative disorder of the GI tract, with normal endoscopy and EBV(+) cells present.

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Case description: 68 year old female with a history of chronic diarrhoea, previously diagnosed with inflammatory bowel disease, diagnosis subsequently changed to irritable bowel syndrome. Patient reported associated bloating, nausea and vomiting and epigastic pain, with 10kg weight loss in last 2 years. HIV negative. No known cause of immunocompromise. No systemic lymphadenopathy.
Upper gastrointestinal endoscopy and colonoscopy normal in 2017 (colonoscopy in 2009 showed abnormal caecum with oedema).
Previous terminal ileum and large bowel series biopsies (2009) reported as showing mild chronic active inflammation with cryptitis, along with mild villous shortening and a single crypt abscess in the terminal ileum. Colon and rectum (2009) biopsies normal.
Due to these previous findings, repeat duodenum, terminal ileum and colon biospies were performed at endoscopy in 2017.
Biopsy fixation details: 5% buffered formalin
Frozen tissue available: No
Details of microscopic findings: Biopsies from the duodenum, terminal ileum and proximal large bowel show expansion of the lamina propria by a dense inflammatory cell infiltrate, predominantly composed of small, minimally atypical, lymphoid cells, with small numbers of plasma cells. The majority of lymphoid cells are T-cells, with CD8(+) T-cells greatly exceeding CD4(+) T-cells.
The small bowel mucosa shows normal villous architecture, with no excess of intra-epithelial lymphocytes. Within the more distal large bowel, crypt architecture is normal, with maintained inflammatory cell gradient in the lamina propria, but a disproportionate number of CD8(+) T-cells.
Immunophenotype: Positive markers (in T-cells): CD2, CD3, CD5, CD7, TIA1, TCRab, granzyme B (subset), CD103 (subset). CD8(+) T-cells greatly exceeding CD4(+) T-cells.
Negative markers (in T-cells): CD25, CD30, perforin, CD56, CD57
MIB1-positive proliferative fraction <10% in the lymphoid cells. EBER(ISH) postive in occasional cells.
Cytogenetics: None performed.
Molecular studies: TCR gene rearrangement studies (Biomed 2 priemrs) performed on 2017 biopsy, shows clonal patterns with the BC1 and GB primer sets (peak sizes 308nt and 177nt respectively).
TCR gene rearrangement studies performed on 2009 biopsy retrospectively, showed the same clonal peak in the GB primer set (only one replicate available and no other interpretable amplifications).
Proposed diagnosis: Indolent CD8(+) T-cell lymphoproliferative disorder of the GI tract.
Interesting feature(s) of submitted case: - This is a relatively rare diagnosis (only 10 cases in the literature)
- It remains a provisional entity in WHO 2016 classification
- This case differs from those described in the literature with respect to normal endoscopy findings and EBER(ISH) positive cells present.
- Cases in the literature all record abnormal endoscopy
- Cases in the literature all report EBV being negative (where tested)
- This patient's EBV viral load was just under log 4, with serology consistent with past primary EBV infection. EBER(ISH) postive cells interpreted as bystander cells, and this was not considered to be an EBV-driven lymphoproliferative disorder.
- The presence of increased CD8(+) T-cells in 2009 along with the same clonal peak, supports the indolent nature of this pathology.

Reference: R Matnani et al. Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract; a review and update. Haematol Oncol 2017;35:3-16.

EAHP18-LYWS-163

A rare chronic case of CD4-positive indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

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Case description: A 50-year-old man from China was referred to our institution in 2015 with more than 20 years history of slowly progressive postprandial abdominal bloating, discomfort, constipation, and distention. Initially his symptoms were managed with laxatives and later he was hospitalized several times with incomplete bowel obstruction and managed conservatively. He lost 2 to 3 kgs of weight and denied history of melena or fever. He had extensive evaluation in his home country, including upper and lower endoscopy with biopsy showing esophagitis, and chronic superficial reflux gastritis. Terminal ileum biopsies showed chronic inflammation, erosion, lymphocytic infiltration but were not felt to be diagnostic.
In 2015, his CBC was normal and extensive evaluation for celiac disease, autoimmune disease and infection including HIV, HTLV, and tuberculosis were negative. Upper endoscopy and colonoscopy were unremarkable. CT enterography showed diffuse small bowel distention and mild small bowel wall thickening and mild small bowel mesenteric lymphadenopathy. Biopsies are described below. He has been treated with budesonide with some symptomatic relief. In 2017, he developed a CMV enteritis-related perforation and underwent resection of 1m of small bowel in China. Residual lymphoproliferative disorder was present in this specimen as well as annual surveillance biopsies.
Biopsy fixation details: Small bowel (duodenum and jejunum): formalin
Frozen tissue available: NA
Details of microscopic findings: Lamina propria is expanded with dense non-destructive mature appearing lymphocytes. Eosinophils are also present. There are no granulomas.
Immunophenotype: T-cells are positive for CD3, CD4, CD2, CD5, CD7, and TCR betaF1 and negative for TCR-delta, TIA1, granzyme B, CD56, and EBV-ISH.
Cytogenetics: NA
Molecular studies: Clonal T-cell receptor gene rearrangement detected.
NGS: ATM (pY1248C) VAF 46.8% ; EZH2 (pA622P) VAF 26.5%
Proposed diagnosis: CD4-positive indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Interesting feature(s) of submitted case: Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (GIT) was first described by Carbonnel et al in 1994.[1] These patients have a chronic course with disease mostly confined to GIT; usually involving small bowel but also can involve colon, oral cavity and esophagus. Often these cases are diagnosed as celiac sprue with no improvement of symptoms with gluten free diet.[3] Patients can have involvement of regional lymph nodes, as in our case, but systemic lymphadenopathy is not commonly seen.[4] Histologically, the mucosal infiltrates have bland looking T-cells with mature T-cell immunophenotype, which makes it difficult to differentiate from normal lamina propria cells, causing a diagnostic difficulty, often for many years, as in our case.
Clonal T-cell receptor gene rearrangements are present, potentially leading to the pitfall of over-diagnosing this indolent lesion as peripheral T cell lymphoma. Pathologic keys to recognition are the bland nature of the infiltrate and lack of tissue destruction. Clinical features of chronicity as well as the lack of a destructive lesion on endoscopy are also useful features.
Large-scale genomic studies on this lesion are sparse, likely due to the rarity of the lesion and indolent nature. However, it is clear that these lesions are negative for STAT3 mutations, suggesting they are not directly analogous to T cell large granular lymphocytic leukemia. [2,4] Our case had NGS performed in China for a panel of lymphoma-related genes which identified mutations in EZH2 and ATM.

EAHP18-LYWS-174

CD4+ Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

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Case description: A 50 year old female with 3 years of diarrhea, bloating, and weight loss was referred for management of seronegative celiac disease. Chemistries and peripheral blood indices were normal. Endoscopy showed diffuse congestion, friability, nodularity, and scalloping of the duodenum. Mild mesenteric lymphadenopathy was noted on CT scan. Biopsies of stomach, duodenum, ileum, and colon revealed an indolent T-cell lymphoproliferative disorder (LPD) of the GI tract. Staging bone marrow biopsy performed 17 months later did not show morphologic evidence of disease, however cytogenetic analysis indicated minimal marrow involvement by LPD. Over the past 6 years, the patient has been treated with budesonide, romidepsin, and pralatrexate, with some improvement in symptoms, but endoscopy and imaging have shown persistent disease.
Biopsy fixation details: Formalin
Frozen tissue available: Yes
Details of microscopic findings: Duodenal biopsy showed crypt hyperplasia, variable villous atrophy, and minimal intraepithelial lymphocytosis. A dense lymphocytic infiltrate was seen in the lamina propria, along with scattered plasma cells and eosinophils. The lymphocytes were mostly small and had oval or angulated nuclei, fine chromatin, indistinct nucleoli, and scant to moderate clear cytoplasm. Clusters of lymphocytes were seen infiltrating crypt epithelium (lymphoepithelial lesions). Mild, patchy infiltration was also seen in gastric, ileal, and colonic biopsies.
Immunophenotype: The LPD showed the following immunophenotype: CD2+, CD3+, CD5+, CD7+/-, CD4+, CD8-, CD30-, TCRαβ+, CD103-, FOXP3-, BCL6-, PD1-, TIA1-, granzyme B-, and perforin-. The Ki-67 labeling index was low (5%). Clusters of lymphocytes within crypts showed the same phenotype. Scattered CD8+ T-cells, CD20+ B-cells, and occasional lymphoid follicles were noted in the lamina propria.
Cytogenetics: G-band karyotyping of duodenal tissue showed: 46,XX,t(9;17)(p22-23;q12)[1]/45,idem,-X[19]. FISH analysis using XY probes showed loss of one X chromosome in 66% of cells. Karyotyping of the peripheral blood showed a normal female karyotype. Karyotyping of the bone marrow aspirate (72 hr. PHA-stimulated culture) showed: 46,XX,t(9;17)(p22-23;q12)[1]/45,idem,-X[2]/46,XX[17]. FISH analysis showed loss of X in 3% of cells. Analysis of subsequent duodenal biopsies (14 months later) showed evidence of clonal evolution/progression: 46,XX,t(9;17)(p22-23;q12)[1]/45,idem,-X[16]/45,idem,-X,del(9)(q22q34)[2]/46,XX[1].
Molecular studies: Targeted next-generation sequencing of 465 cancer-associated genes revealed no somatic mutations. T-cell receptor-β gene rearrangement analysis showed the same-sized clonal rearrangement in the stomach, duodenum, jejunum, ileum, and right colon. However, analysis of the blood and marrow aspirate did not detect any clonal products.
Proposed diagnosis: CD4+ Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract.
Interesting feature(s) of submitted case: Indolent T-cell LPDs of the GI tract are rare clonal lymphocytic proliferations of mucosal CD4+ or CD8+ (and rarely CD4- CD8-) T-cells that are often misdiagnosed as inflammatory disorders (celiac disease as in this case). Our case highlights the use of conservative management in disease control. These LPDs are thought to be localized to the GI tract for protracted periods, with rare cases showing systemic dissemination late in disease course, however detection of a minor clone in the bone marrow of our patient with the same cytogenetic abnormality as in the duodenum, shortly after disease diagnosis, indicates that systemic dissemination of neoplastic lymphocytes may occur early in some cases.

EAHP18-LYWS-180

Monomorphic epitheliotropic intestinal T-cell lymphoma

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Case description: A 75-year old female presented with abdominal distention, pain, and intestinal obstruction due to ileal tumor. No history of diarrhea and coeliac disease. Physical examination showed no mass and no lymphadenopathy in other site. Small intestinal resection was performed. Macroscopically, the tumor measured 4x4x2 cm, bulging into the serous layer, whitish and rubbery in consistency. LDH level was within normal range (308 U/L). The non-tumorous mucosa showed no marked abnormality. HLA typing was not done.
Biopsy fixation details: 10% neutral buffered-formalin for 12 hours
Frozen tissue available: N/A
Details of microscopic findings: Ileal tissue resection showed diffuse transmural proliferation of monotonous medium-sized lymphoid cells with dispersed chromatin, inconspicuous nucleoli and clear cytoplasms. The tumor lacked inflammatory infiltrates. The adjacent mucosa showed blunting villi and ulceration. There was also epitheliotropism characterized by infiltration of lymphocytes in the epithelium. No enteropathy changes (crypt hyperplasia and villous atrophy) were found.
Immunophenotype: The tumor cells were positive for CD 3, CD 7, CD 56, TIA1 and perforin. Ki67 proliferation index was 70%. Other markers such as CD 8, CD 4, CD 30, CD 5, CD 20, CD 79a, CD 10, granzyme B and EBER ISH were all negative. Several important markers (MATK, CD 103, TCRαβ, TCRγδ) were not available in our laboratory.
Cytogenetics: N/A
Molecular studies: N/A
Proposed diagnosis: Intestinal T-cell lymphoma, in favor of monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).

Interesting feature(s) of submitted case: MEITL is a rare type of lymphoma and it is more common in Asian population such as in our country. Our case was a female while some studies reported of male predominance. The tumor located in a single site of small intestine, as expected. The morphology and immunophenotypic features were in concordance with the literatures. The typical monomorphic tumor cells, epitheliotropic and the positivity of CD 3, CD 7, CD 56, cytotoxic granules in addition of negative EBER confirmed the diagnosis. However in this case there was loss of CD 8 expression, which can occur in the small proportion of the reported MEITL cases. Further immunohistochemistry staining and molecular examination are necessary to confirm the diagnosis.

EAHP18-LYWS-181

Intestinal T-cell lymphoma diagnosed as monomorphic epitheliotropic intestinal T-cell lymphoma with an unusual immunophenotype.

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Case description: A 37-year-old formerly healthy male presented with acute onset of abdominal pain, elevated temperature (39.5°C), discrete leukocytosis (9.9x10^9/L) with monocytes in the upper reference interval (0.9x10^9/L) but the differential was otherwise normal, and an elevated C-reactive protein. Other blood parameters were normal. Examination by CT with contrast demonstrated segmental thickening of the walls of the small bowels and discrete abdominal lymphadenopathy. No hepatosplenomegaly was noted. An explorative laparoscopy was performed and thickened segments of the ileum and jejunum were excised. Pathologic examination of the tissue samples demonstrated an intestinal T-cell lymphoma primarily diagnosed as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL, formerly EATL type II). No involvement of bone marrow or blood by the T-cell lymphoma was found and apart from the intestinal foci and the enlarged abdominal lymph nodes no other suspicious sites of lymphoma infiltration was noted on CT. Ann Arbor staging 1-2. The patient went through 6 cycles of CHOEP14 treatment, followed by high dose treatment with BEAM (carmustine, etoposide, cytarabine, and melphalan) with autologous stem cell support. The patient was considered to be in remission, but relapsed 8 months later histologically confirmed lymph node metastases and lymphoma infiltration of the bone marrow. The disease progressed despite second line treatment with GDP (gemcitabine, dexamethasone, and cisplatin) and haploidentical stem cell transplantation could not be initiated. The patient finally succumbed to his disease 19 months after diagnosis.
Biopsy fixation details: Fixated in 4% formaldehyde.
Frozen tissue available: No.
Details of microscopic findings: Microscopically the tissue section represents part of the ileum wall with a transmural monomorphic cellular infiltrate consisting of middle sized lymphoid cells with round nuclei and a rim of pale cytoplasm. Part of the surface of the section is covered with intestinal epithelium, and only few scattered acini remains in the lamina propriae due to the lymphoid infiltrate. Epitheliotropism is noted. There are also foci of ulcerations including acute inflammation where the epithelium is eroded. The proliferation index (ki67) is 34 %.
Immunophenotype: Flow cytometry: mCD3-/cyCD3+/CD5-/CD7+/CD2-/CD8dim/-/CD4-/CD20dim/cyCD79A+subpop/CD38+/CD56+subpop/CD57-/CD45+
Immunohistochemistry: CD3+/CD5-/CD7+/CD2-/CD4-/CD8-/CD30-/CD20dim/CD79A-/PAX5-/EBER-/CD56+/TIA-1+/GranzymeB+/TCRab-

Cytogenetics: No.
Molecular studies: PCR-analysis demonstrated monoclonal rearrangements of the TCR-beta, TCR-gamma and TCR-delta genes. No detectable monoclonal rearrangements of IgH could be demonstrated.
Proposed diagnosis: Monomorphic Epiteliotropic Intestinal T-cell lymphoma (MEITL).
Interesting feature(s) of submitted case: This is a case of the uncommon T-cell lymphoma MEITL (monomorphic epitheliotropic intestinal T-cell lymphoma) with an unusal immunophenotype. MEITL is most commonly CD8+, but this case lacks CD8. A differential diagnosis of extranodal NK/T-lymphoma was considered, but since monoclonal rearrangements of the TCR-beta, TCR-gamma and TCR-delta genes, cytoplasmatic CD3-positivity and EBV-negativity was noted, this diagnosis was considered unlikely. Further, hepatosplenic T-cells lymphoma was discounted due to lack of hepatosplenomegaly at diagnosis and no bone marrow involvement. The patient did not have a history of coeliac disease and the lymphoid infiltrate was monomorphic and therefore EATL was also discounted.

EAHP18-LYWS-224

Topic: LPD in gastrointestinal tract, excluding gastric marginal zone lymphoma

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Case description: 66 year-old man, with a history of low platelet count, lymphocytosis, and splenomegaly; a dignosis of Hairy Cell Leukemia was made on a bone marrow biopsy. After the first administration of cladribine, the patient developed fever, ascites and ileal perforation. The diseased ileum was surgically resected (sample shown). After one month the patient died.
Biopsy fixation details: Bone marrow biopsy specimen was fixed in B5 solution for 2 h and then decalcified in an EDTA-based solution for 2.5 h.
Ileal specimen: 10% buffered formalin fixation for 24h and paraffin embedding
Frozen tissue available: not available.
Details of microscopic findings: BONE MARROW: 60% cellularity; massive infiltrate consistent with hairy cell leukaemia involving more than 80% of the cellularity; residual haemopoiesis predominantly represented by erythropoiesis;
ILEUM: diffuse transmural proliferation of mediun size lymphocytes with mononorphic appearance, with prominent epitheliotropism; no/minimal inflammatory background and necrosis.
Immunophenotype: BONE MARROW: CD20+, annexin A1+, CD200+, DBA44+, CD3-, CD2-, CD8-, CD56-
ILEUM: CD20-, Annexin A1-, BetaF1+, TCRgamma likely positive (more doubtful results), CD2+, CD7+, CD8+, CD56+, Tia1+, CD5-, CD4-, CD30-, Perforin-, Granzyme B -, KI67 60%.
Cytogenetics: No cytogenetics assays were performed.
Molecular studies: PERIPHERAL BLOOD:
BRAFV600E mutation (digital PCR): mutated with 38% allele frequency
ILEUM:
1) BRAFV600E mutation (pyrosequencing; 599-601 custom): mutated with 48% allele frequency
Proposed diagnosis: Intestinal T-cell lymphoma, more consistent with monomorphic epiteliotropic type, with BRAFV600E mutation in a patient affected by BRAFV600E mutated Hairy Cell Leukaemia.
Interesting feature(s) of submitted case: The interesting feature of this case is the presence of the same somatic BRAFV600E mutation in two simultaneous lymphoid neoplasms of different lineage. No identical cases reported; exceptional reports of non–intestinal T-cell lymphoma and Hairy Cell Leukaemia
Possible hypothesis: 1) common stem cell progenitor or 2) transdifferentiation.

EAHP18-LYWS-227

Topic: LPD in gastrointestinal tract, excluding gastric marginal zone lymphoma

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Case description: Case description: Male, 57 years, no coeliac disease; due to long standing diarrhea and weight loss the patient underwent colonoscopy (2012) which revealed isolated ulcers throughout the gross intestine suggesting Crohn's disease. Tree biopsies were performed and resulted suggestive for Crohn disease. Steroids were administered with partial clinical response.
In May 2016 the patient arrived at our hospital and a colonoscopy showed persistency of the ulcers lesions as well as colic diameter reduction. Due to a "wax and wane" clinics, steroids were administered discontinuously and stopped few months later. The ulcers were confirmed in the subsequent 2016 colonic biopsy.
The patient was off therapy in March 2017 (last follow up colonic biopsy) which found no clear cut active disease.
Biopsy fixation details: 10% buffered formalin fixation for 24h and paraffin embedding
Frozen tissue available: Not available
Details of microscopic findings: Focal rather wide areas of medium-sized cells, with irregular nuclear profile, incospicuous nucleoli and variably large pale cytoplasm. The non involved mucosal areas showed mild chronic non-specific inflammation. No clear cut features for Crohn's disease.
Immunophenotype: CD3+, CD20-, CD4-, CD8-, CD56+, Tia1+, CD5-, CD7+; Ki67 variable (focally 35-40%) TCR-gamma-, TCR αβ-
Cytogenetics: No cytogenetics assays were performed.
Molecular studies:
PCR (EUROCLONALITY protocols)
TCR-gamma: policlonal
Proposed diagnosis: NK cell enteropathy
Interesting feature(s) of submitted case: The case resembles those described by Mansoor et al (Blood 2011) or Takeuchi et al (Blood 2010) but our case showed a self limiting course despite a relatively high proliferation index.

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CLONAL INDOLENT T CELL LYMPHOPROLIFERATIVE DISORDER OF GI TRACT

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Case description: A 71-year-old male presented (2014) with a long standing history of persistent diarrhea and significant weight loss. A lower GI endoscopy revealed multiple small polyps extending from the ileum to the rectum. One of the colonic polyps was biopsied.
He had been investigated in the past (in 2006 & in 2010) for similar complaints. On both occasions a colonic biopsy was carried out.
A CT scan in 2014 showed mild hepato-splenomegaly and mesenteric adenopathy.
He has been treated all along with Azathioprine and corticosteroids for a presumptive diagnosis of ulcerative colitis. At some point he received a brief empirical course of anti-tuberculous medication.
Biopsy fixation details: This was a case recieved in consult, the referring pathologist informs that the tissue was fixed in 10% formalin and subsequently paraffin embedding and routine processing in alcohol was carried out.
Frozen tissue available: None.
Details of microscopic findings: All three colonic biopsies revealed an almost similar morphology – that of a lymphoid infiltrate composed of medium sized lymphocytes expanding the lamina propria and displacing the crypts. However, there was no evidence of crypt invasion, cryptitis or significant distortion of crypt architecture. The lymphoid cells had mature nuclear chromatin, inconspicuous nucleoli and a moderate amount of eosinophilic to clear cytoplasm. Mitotic figures were hard to find. An infiltrate of eosinophils also accompanied the lymphoid cells.
Immunophenotype: The colonic biopsy of 2006 was not available for review, but was reported to show an atypical T cell lymphoid infiltrate.
The colonic biopsy of 2010 also showed an atypical lymphoid infiltrate. The lymphoid cells expressed CD3, CD2, CD7, CD8 and TIA-1 and were immunonegative for CD20, CD5, CD4, CD30, CD56, granzyme B and EBER-ISH.
The colonic biopsy of 2014 had a similar immunoprofile, with the additional findings of TCR-BF1 expression in the tumor cells & a proliferation fraction of < 5% as assessed by MIB1 immunostaining.
Cytogenetics: none
Molecular studies: Clonality analysis with BIOMED primer sets was carried out on the biopsies from 2010 & 2014 respectively at the time of diagnosis. Both results showed IgH in germline and rearrangements in beta & gamma chains of T cell receptor.
Proposed diagnosis: On both occasions in 2006 & 2010, a diagnosis of T cell lymphoma was rendered based on the immunoprofile (in particular the loss of CD5 together with a CD8 restricted population of T cells) This diagnosis was further strengthened in 2010, when clonality analysis showed a clonal T cell gene receptor rearrangement.
When the biopsy & molecular findings in 2014 once again pointed to a diagnosis of a T cell lymphoma, the fact that the patient had done rather well, albeit that he was symptomatic, and had no disease progression for 8 years despite not receiving therapy for a T cell lymphoma, prompted us to look at the case afresh.
At about the same time, a description of similar indolent T cell “lymphoproliferations” of the GI tract appeared in the literature (Blood 2013,122;3599-3606) and we concluded that this case was indeed a clonal Indolent T cell lymphoproliferative disorder of the GI tract.
Interesting feature(s) of submitted case: This case is interesting because the natural history, morphology and immunophenotype could be observed over a period of 96 months, during which period the patient did not receive conventional therapy for a peripheral T cell lymphoma. Moreover, Azathioprine and corticosteroid therapy appeared to have no effect on the natural course of the disease. The patient remains symptomatic but has no disease outside of the gastrointestinal tract.

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Monomorphic epitheliotropic intestinal T-cell lymphoma in a 77-year-old female

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Case description: A 77-year-old female presented with a history of nausea and mild abdominal pain. An upper gastrointestinal endoscopic examination 5 years previously had been normal. An abdominal CT scan was normal at presentation, and she underwent upper and lower GI endoscopy. This endoscopic examination revealed mild gastric erythema and normal-appearing duodenal and colonic mucosa. Gastric and duodenal biopsies were obtained. The duodenal biopsy demonstrated increased intraepethelial lymphocytes, without significant villous blunting, and a diagnosis of celiac disease was suggested. No phenotypic assessment of the lymphocytes was performed at this time. Subsequent serologic studies did not support a diagnosis of celiac disease. The patient continued to have vague pain and had an unexplained weight loss of 20 pounds over the next several months. Eight months after the initial biopsy, she had a second CT scan that revealed abnormal colonic wall thickening and a 9 cm mass in the liver. Colonic and liver biopsies were performed and sent for review. The prior duodenal biopsy was re-examined in light of the colon and liver findings. A staging bone marrow examination was negative for lymphoma. Following her diagnosis, the patient was treated with 2 cycles of CHOP; however, she experienced disease progression and respiratory failure. She died two months following the diagnosis of lymphoma.
Biopsy fixation details: Formalin
Frozen tissue available: No
Details of microscopic findings: Duodenal Biopsy: There are markedly increased intraepithelial lymphocytes, predominantly of small size, with some nuclear atypia and ample cytoplasm. The lymphocytes extend deep into the crypts, and villous blunting is only focal.
Colonic Biopsy: Ulcerated mucosa with an intraepithelial and lamina propria infiltrate of morphologically atypical lymphocytes, most of intermediate to large size. Some eosinophils and neutrophils are present in the background.
Liver Biopsy: Effaced by sheets of morphologically abnormal lymphocytes, similar to those seen in the colonic biopsy. No residual liver parenchyma was present in the biopsy specimen; some background eosinophils are present.
Immunophenotype: Duodenal Biopsy: A limited panel was performed. The lymphocytes were positive for CD3, CD8, CD56, and TIA1; negative for CD4.
Colonic Biopsy: The lymphocytes were positive for CD3, CD7, CD8 (weak, in a subset), TCR delta, CD56, TIA1, Granzyme B (in a subset); negative for CD2, CD4, CD5, TCR BF1, ALK, CD30, CD25, LMP1, EBER-ISH, and CD20.
Liver Biopsy: A limited panel was performed. The lymphocytes were positive for CD3, TIA1, CD8 (minor subset), and Granzyme B (minor subset); negative for CD4 and CD20.
Cytogenetics: No
Molecular studies: No
Proposed diagnosis: Monomorphic epitheliotropic intestinal T-cell lymphoma
Interesting feature(s) of submitted case: This case illustrates the importance of phenotypic characterization of intestinal biopsies with marked intraepithelial lymphocytosis. Although the intraepithelial lymphocytes present in the patient's initial duodenal biopsy are not as morphologically malignant-appearing as were those present in her subsequent colonic and liver biopsies, the discordance between the degree of lymphocytosis and the lack of villous blunting and other features of celiac disease should have prompted phenotypic characterization. This example of MEITL illustrates the presence of a gamma-delta phenotype and more morphologic pleomorphism than is seen in some cases. It also illustrates subtle differences in phenotype (predominantly CD8 expression) between the neoplastic cells in the tumorous mass lesion and distal areas with intraepithelial involvement.

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Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

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Case description: 60-year-old male, active photographer, presented with a history of diarrhea, abdominal distention, pain and weight loss since 1993. Gluten free diet did not help. In 1998, a colonoscopy suggested Crohn's disease. He underwent ileocaecal resection (2001) and was diagnosed with quiescent Crohn's disease. He received mesalamine and azathioprine but did not improve. Steroids and antibiotics were somewhat effective.
In 2003 he had flare of his symptoms, and was found to have partial small bowel obstruction. He underwent laparotomy and a full- thickness small bowel biopsy, which was diagnosed as a "small T-cell lymphoproliferative disorder". A second transmural intestinal biopsy (3 months later), had similar findings. A positive TCR gamma clone was seen on both occasions and was diagnosed as an "enteropathy type T-cell lymphoma with atypical phenotype." A bone marrow biopsy (2003) was unremarkable. The patient was treated with chemotherapy (CHOP) but did not improve. Multiple upper GI endoscopy and enteroscopy procedures were performed over the years and were reported to be normal (2002, 2004, 2007) or to demonstrate gastric erythema and flattened duodenal and/ or jejunal mucosa (2009, 2011, 2012). After 2003, he was not treated with chemotherapy in spite of the persistent infiltrate with clonal T-cells; but was managed with low dose steroids and antibiotics for bacterial overgrowth. He was rebiopsied in 2017, >13 years after the initial diagnosis. Endoscopy in 2017 demonstrated only some duodenal mucosal flattening.
Biopsy fixation details: Formalin
Frozen tissue available: no
Details of microscopic findings: Full thickness small bowel biopsy from 2003 demonstrates some blunting of the villi and increase in intraepithelial lymphocytes, and a relatively superficial band like lymphoid infiltrate in most areas but in focal areas the infiltrate extended through the muscularis propria. The lymphoid cells were relatively small and monotonous. Multiple superficial endoscopic intestinal biopsies demonstrated similar non-destructive lymphoid infiltrate with a similar TRG clone over the next 9 years. No increase in intraepithelial lymphocytes was seen in these biopsies.
Immunophenotype: CD3+, CD5+, CD2+, CD7+, mostly CD8+, CD56-, EBER-, CD30-, Beta F1+, Ki67 – very low
Cytogenetics: NA
Molecular studies: TCR gamma gene rearrangement was positive on multiple occasions (2003X2, 2004, 2005, 2007, 2009, and 2012) with a leading edge band in the V1-8 region on all occasions. TCR gamma and beta studies (2017) using BIOMED-2 primers were positive. Although the TCR gamma studies could not be compared directly (the clonal band was not sized in any assay except the 2017 study), there was always a clonal product seen in the V1-8 region.
Proposed diagnosis: Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract.
Interesting feature(s) of submitted case: Primary T-cell lymphomas of the GI tract are rare and usually aggressive. This case illustrates an indolent persistent lymphoid proliferation in the GI tract composed of small lymphoid T-cells with positive T-cell receptor gene rearrangement studies. The morphologic findings and the clinical course are thought to best fit into the provisional WHO2016 category of "**Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract"** although the infiltrate seemed to be deeper than usually described in the full thickness 2003 biopsy. This case highlights the importance of recognizing this new provisional entity. It illustrates how chemotherapy is not efficacious and its indolent course inspite of the clonal TCR gene rearrangement and sometimes extention beyond lamina propria.

EAHP18-LYWS-307

Aggressive lymphoma of the GI tract in a patient with a history of marginal zone lymphoma: a broad differential diagnosis harnessing histologic cues yields unexpected diagnosis of an unusual lymphoma, corroborated by subsequently obtained history (!)

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Case description: An 80-year-old male with history of nodal marginal zone lymphoma (diagnosed six years previously and never treated) presented with abdominal pain, and was diagnosed with intestinal perforation. A small bowel resection was performed.
Biopsy fixation details: Formalin-fixed, paraffin embedded.
Frozen tissue available: Unavailable
Details of microscopic findings: H&E stained sections show a diffuse and destructive transmural atypical infiltrate with ulceration, serositis, and necrosis. The infiltrate consists predominantly of large atypical mononuclear cells with irregular nuclei, vesicular chromatin and prominent nucleoli. Scattered small lymphocytes, plasma cells and eosinophils are noted in the background. Nodules of small lymphocytes are also noted. In uninvolved areas, the intestinal mucosa demonstrates an increase in intraepithelial lymphocytes, which is most prominent at the tips of villi.
Immunophenotype: Immunostains demonstrate that the large atypical cells are positive for CD3, TCR-gamma, perforin, granzyme B and CD30. CD2, CD4, CD5, CD7, CD8, CD56, CD57, TCR-beta, ALK, PD1, PAX5, CD10, BCL6, MUM1, and EBER1 are negative. The scattered nodules consist of CD20+ CD79a+ B-cells that are negative for CD10, BCL6, CCND1, and MUM1.
Cytogenetics: N/A
Molecular studies: TRG PCR demonstrates a monoclonal rearrangement (188 bp peak) using Vgamma 9-11 primers. IGH PCR demonstrates a monoclonal rearrangement with FR2 and FR3 primers (247 and 91 bp, respectively).
Proposed diagnosis: Enteropathy Associated T-Cell Lymphoma (EATL), with an unusual immunophenotype
Interesting feature(s) of submitted case: Based on the morphologic findings, the initial diagnostic consideration in this patient with a history of a small B cell lymphoma was transformation to diffuse large B-cell lymphoma. However, the lymphoma was CD3+ and lacked B-cell antigens. In the uninvolved mucosa, there was marked intraepithelial lymphocytosis and villous blunting, hallmarks of gluten-sensitive enteropathy; although no history of this was provided at the time of submission of this consultation case, one was subsequently obtained. Hence, a diagnosis of enteropathy associated T-cell lymphoma seemed likely. Typically, the immunophenotype of EATL is that of an alpha-beta+ cytotoxic T-cell that lacks expression of CD5, CD8 and CD56. The strong CD30 expression in a substantial proportion of the neoplastic cells raised the differential diagnosis of anaplastic large cell lymphoma. Further, the neoplastic cells strongly expressed TCR-gamma, an unusual finding in EATL, and more compatible with monomorphic epitheliotropic intestinal T-cell lymphoma. Finally, there were small nodules of B-cells both within and outside the T cell infiltrate, raising the possibility of the subtle background presence of the previously diagnosed marginal zone lymphoma. Molecular studies showed a monoclonal rearrangement of IGH (and TRG), lending further support to concomitant involvement by a clonal B-cell process.

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Enteropathy-associated T-cell lymphoma with anaplastic features

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Case description: A 62-year old Caucasian man with history of recent gastritis presented with acute abdominal pain for 2 days. His past medical history is significant for Type II diabetes mellitus and hypertension. He experienced diarrhea for the last 2 years with increasing abdominal pain in the last 2 weeks and lost 60 lbs over 6 months. The patient underwent colonoscopy and EGD 2 days prior to admission and gastritis with small bowel ulceration has been diagnosed. He was was started on omeprazole and amoxicillin for treatment of presumed H. pylori gastritis however he developed an acute onset of abdominal pain 2 days later and was brought to the Emergency Department. Chest X-ray demonstrated free air in the abdomen and the patient underwent exploratory laparotomy. Perforation of small bowel and multiple small bowel masses were noted and small bowel resection was performed.
Biopsy fixation details: Sections of the specimen were fixed in formalin.
Frozen tissue available: No.
Details of microscopic findings: H&E stained sections shows epitheliotropic lymphoid tumor infiltrate involving the entire small bowel (jejunum) wall thickness from mucosa to serosa and fat. Villous blunting and crypt hyperplasia are noted in the involved and uninvolved sections of jejunum. The neoplastic cells are medium to large-sized and have markedly irregular, frequently angulated nuclei, moderately dispersed chromatin and occasional prominent nucleoli, and scant to moderate amounts of clear to eosinophilic cytoplasm. Frequent very large bizarre cells with irregular hyperchormatic nuclei, occasional multinucleation and occasional prominent nucleoli, and moderate amounts of amphophilic cytoplasm are noted. The tumor infiltrate is frequently angiocentric an angionivasive and perineural invasion is also noted. Focally the mucosa is ulcerated. There are also extensive areas of tumor necrosis in the bowel wall. The adjacent uninvolved mucosa shows prominent villous blunting and crypt hyperplasia and increase in intraepithelial lymphocytes (IEL). There is increased inflammatory infiltrate in the submucosa composed of small mature lymphocytes, plasma cells and eosinophils. In addition small lymphoid aggregates are seen in the lamina propria. No metastatic tumor is identified in adjacent lymph nodes with sinus histiocytosis.
Immunophenotype: Immunohistochemistry staining shows that the neoplastic cells are CD2+ CD3+ CD7+ CD30+ CD43+ CD45+ MUM1+ BCL6(dim subset)+ granzyme B+, perforin+ TCR-delta+ clusterin+ EMA+ and focally TIA-1+. The proliferation index (Ki67+) is approximately 80%. They are CD4- CD5- CD8- CD10- CD20- CD56- CD57- TCR-beta- TCR-gamma- ALK1-. EBER-ISH -. The IEL in the adjacent uninvolved mucosa are CD3+ CD4- CD8- and CD56-.
Flow cytometric analysis of the small bowel mass is suboptimal due to inadequate numbers of viable cells (18%) but revealed a small population of CD103+ T cells (20% of the region, 1% of total events).
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Enteropathy-associated T-cell lymphoma (EATL), anaplastic variant.
Interesting feature(s) of submitted case: This EATL has anaplastic morphology with a wide spectrum of cytologic atypia and expression of CD30, TCR-delta and CD103 (by flow) by the malignant cells. There is prominent angiocentricity and angioinvasion and perineural invasion. The significant villous blunting, crypt hyperplasia and increase in IELs and inflammatory infiltrate indicates that this patient was affected by previously undiagnosed refractory celiac disease, likely type 2 and presentation of his celiac disease was concomitant with the diagnosis of EATL.

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NK-cell enteropathy presenting as a gastric polyp

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Case description: The patient is a 65-year old male who presented with symptoms of dyspepsia and reflux. Esophagogastroduodenoscopy (EGD) showed diffuse erythema of the gastric mucosa and a gastric polyp. A polypectomy was performed, disclosing features of NK-cell enteropathy. Random gastric biopsies showed active chronic gastritis positive for H. pylori infection. The patient was treated with proton pump inhibitors and antibiotics, with improvement of symptoms. Repeat biopsy 3-4 months later was negative for persistent disease.
Biopsy fixation details: Neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Sections of the gastric biopsy showed a polypoid lesion with an atypical mononuclear infiltrate in the lamina propria. The gastric glands were widely separated by a monotonous infiltrate of atypical lymphoid cells with abundant pale, clear cytoplasm, distinct cytoplasmic borders, and irregular nuclei with dispersed chromatin. The atypical cells did not invade the glandular epithelium. The adjacent mucosa showed an infiltrate of lymphocytes and plasma cells, with few neutrophils and eosinophils.
Immunophenotype: The atypical cells were positive for CD3 (cytoplasmic), CD56, CD7, TIA-1 with only dim Granzyme B. They were negative for CD2, CD4, CD5, CD8, CD57, CD30, BCL2, TCR gamma. EBER ISH was negative. Other lineage markers were negative including CD20, PAX5, CD10, BCL6, CD21. Ki-67 showed a moderate to high proliferative rate in the atypical cells. PAX5 showed a focal small aggregate of B-cells.
Cytogenetics: Not done
Molecular studies: T-cell gamma gene rearrangement was negative, with a polyclonal pattern.
Proposed diagnosis: NK-cell enteropathy
Interesting feature(s) of submitted case: This is a characteristic case of NK-cell enteropathy. Gastric cases have also been referred to as lymphomatoid gastropathy in Japan. Despite the cytological atypia, the clinical course is benign and self-limited in most patients. The etiology of this lesion is unknown, but may represent a response to unknown antigens/ pathogens. While some patients have had evidence of Helicobacter infection, a definite association has not been shown.

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Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) with aberrant CD20 expression.

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Case description: A 55 old previously healthy man was admitted to emergency in septic shock. Acute surgery was performed due to a small intestine perforation and 5 cm large tumor. Multiple infarcts in the brain were detected at the time of operation. Patient never regained consciousness after operation and died within 1 month from the surgery.
Biopsy fixation details: 4% formalin
Frozen tissue available: no frozen tissue was available
Details of microscopic findings: diffuse infiltration of medium sized lymphocytes engaging full intestinal wall, with mucosal ulceration, intestinal wall destruction and perforation. Epitheliotropism was also seen in the preserved parts of intestine.
Immunophenotype: Lymphoma cells were positive for CD3+, CD8+, CD56+, CD2+, CD7+, Granzyme B+, Bcl-2+, CD20 weak + and negative for PAX5-, CD79a-, CD5-, CD4-, CD30-, Tdt-, CD34-, CD1a-, TIA-1, CD138-, CD57-, TCR a/b-, cyclin D1-, SOX11-, Mum-1-, EBER-, CD10-, Bcl6-. Proliferation detected in Ki67 immunostaining was about 60%.
Intraepithelial lymphocytes in preserved part of small intestine showed slightly different immunophenotype: CD3+, CD8+, CD56+, CD2 dim, CD7+, GRB+, CD5- but were CD20 negative with lower proliferation I Ki67 immunostaining.
Cytogenetics: not done
Molecular studies: PCR showed monoclonal rearrangement of TCR beta and gamma, no rearrangement of IGH and IGK genes.
Proposed diagnosis: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) with aberrant CD20 expression.
Interesting feature(s) of submitted case: The interesting feature of this case is aberrant dim CD20 expression, which can be seen in up to 20% of intestinal T-cell lymphoma cases.
Ref. “CD20 positive cytotoxic T-cell lymphoma: Report of two cases and review of the literature”, Kitamura A. et al., J. Clin. Exp. Hematopathology, 2005.
“Prognostic relevance of CD20 expression in peripheral T-cell lymphomas: a multi-center retrospective study. Toya T. et al, Leukemia & Lymphoma, 2016.

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Intestinal T cell lymphoma?

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Case description: A 51 year old man presented with a history of upper gastrointestinal symptoms. No further past medical history was provided by the clinicians. He underwent upper GI endoscopy at which time biopsies were taken of stomach and duodenum.
Biopsy fixation details: Neutral buffered formalin.
Frozen tissue available: No
Details of microscopic findings: Lamina propria infiltrate of medium sized lymphoid cells.
Immunophenotype: Positive: CD2, CD3. Some loss of CD5 and CD7. Probably CD4 and CD8 negative.
Cytogenetics: None.
Molecular studies: TCR gene rearrangements clonal (BIOMED2 primers)
Proposed diagnosis: Indolent T Lymphoproliferative Disorder of the GI Tract
Interesting feature(s) of submitted case: Newly described entity.

EAHP18-LYWS-427

Monomorphic Epitheliotropic T-cell Lymphoma in a Northern European

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Case description: The patient was a male aged 58 years old when he was admitted with small bowel obstruction and perforation. A perforated segment of small bowel was removed at laparotomy (Dec 2013), submitted for pathological examination and a diagnosis of lymphoma made. Post-operative staging (CT and bone marrow) was negative as was coeliac serology (tissue transglutaminase antibody). Treatment was with four cycles of RIVE followed by autologous stem cell transplant.
The patient remained in complete remission for two years, then presented with a 7 cm mass involving base of penis and scrotum, but CT scan showed no disease elsewhere. Biopsy confirmed relapsed lymphoma which was treated with local radiotherapy with resultant complete resolution. Unfortunately, the patient returned 6 weeks later complaining of anorexia and weight loss with severe persistent nausea and vomiting. Upper GI endoscopy and biopsy showed further relapse throughout the stomach and in the duodenum. At this time, CT scan showed widespread lymphadenopathy. The patient was started on palliative chemotherapy in January 2017, completed with a good partial response. He was well when last seen in clinic at the end of October 2017.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No.
Details of microscopic findings: The wall of small bowel in the area of perforation expanded by diffuse infiltrate of monotonous small to intermediate lymphoid cells. There is little inflammatory background. At the point of perforation the infiltrate extends into the adjacent mesentery. The adjacent mucosa shows relatively intact villous architecture but, in some foci, there is prominent infiltration of epithelium by neoplastic lymphocytes.
Immunophenotype: The neoplastic lymphoid cells display the following phenotype:
Positive: CD2, cCD3, CD7, CD8, CD56, TIA-1
Negative: CD4, CD5, CD30, Granzyme B, Tdt, TCR-beta F1
EBV-ISH (EBER): negative
Cytogenetics: Not done.
Molecular studies: FISH for MYC showed a normal pattern of hybridization.
Proposed diagnosis: MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA
Interesting feature(s) of submitted case: Two main subtypes of intestinal T-cell lymphoma are recognised in the updated 2016 WHO classification of tumours of the haematopoietic and lymphoid tissues; enteropathy associated T-cell lymphoma (EATL) and monomorphic intestinal T-cell lymphoma (MEITL; previously known as type II EATL). Cases of EATL are associated with coeliac disease and are the most common subtype in Northern Europeans. Conversely, MEITL shows no association with coeliac disease and accounts for the majority of intestinal T-cell lymphomas in Asia. However, MEITL has a worldwide distribution, as this case in an indigenous Scot with no serological or clinical evidence of coeliac disease demonstrates, so may be rarely encountered in Northern Europe. The relatively aggressive course with dissemination to other extranodal sites demonstrated in this example is also a feature of MEITL, overall five year survivals of <50% being quoted. Apart from Fish for MYC, molecular genetic studies were not undertaken. However, recent studies highlight the presence of similar genetic abnormalities in EATL and MEITL, e.g. inactivating mutations of SETD2 and mutations affecting the JAK-STAT pathway, particularly in STAT5B (e.g. Moffit AB et al, J Exp Med 2017; 214: 1371-1386), in MEITL. This suggests that, differing associations with coeliac disease notwithstanding, similar pathogenetic mechanisms are at work in both entities.

EAHP18-LYWS-432

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) of TCR alpha/beta derivation, CD56 negative with STAT5B mutation.

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Case description: A 65-year-old woman from Croatia presented with diarrhea and 15 kg weight loss in a three-month period. The patient complained of upper abdominal pain and up to five watery stools a day. Laboratory studies demonstrated megalobastic anemia and B12 deficiency. Serology for celiac disease was negative. Imaging studies revealed segmental stenosis and paresis of ileum and mesenterial lymphadenopathy. A 15 cm small intestinal segment was resected and two lymph nodes measuring 1.5 and 0.8 cm.
Biopsy fixation details: 4% buffered formalin
Frozen tissue available: Not available
Details of microscopic findings: Macroscopic findings: The mucosa was focally ulcerated without a detectable mass and the entire mucosa looked granulated with erythema.
Microscopic findings: The small intestine showed a lymphoid infiltrate invading the intestinal wall going from the mucosa to the serosa. There were ulcers alternating with areas of atrophic villi and hyperplastic crypts reminiscent of celiac disease. There was little epidermotropism in the surface epithelium; however, there was clear epiteliotropism in the crypts. Cytologically the infiltrate was monotonous with small cells with round nuclei, inconspicuous nucleolus and clear cytoplasm. The lymph nodes showed follicular hyperplasia.
Immunophenotype: The tumor cells were positive for CD3, CD8, TIA1, and TCR alpha-beta, but negative for CD56, CD4, CD5, CD30, CD20, granzyme B and TCR gamma-delta. The proliferation index of the tumor was around 10%, as shown by MiB1.
Cytogenetics: no
Molecular studies: A custom AmpliSeq panel (STAT3, STAT5B, JAK3, DDX3X, TP53, MGA, MSN and BCOR) was applied using Ion Torrent PGM Sequencer. The mean coverage was 9030 reads. A somatic mutation of STAT5B in exon 18, p.N642H; c.1924A>C, with a 32% variant allele frequency (VAF) was identified. The mutational analysis of SETD2 is pending. TCR gene rearrangement analysis demonstrated a monoclonal population.
Proposed diagnosis: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) of TCR alpha/beta derivation, CD56 negative with activating STAT5B mutation
Interesting feature(s) of submitted case: 1) The 2016 revised WHO classification recognizes two distinct entities; enteropathy associated T-cell lymphomas (EATL) and monomorphic epitheliotropic intestinal T-cell lymphomas (MEITL). Both disorders have characteristic clinical, morphological and molecular features, although sometimes might have overlapping features. The case presented here has some clinical and morphological features reminiscent of celiac disease, however, the negative serology, the cytological features, immunophenotype and molecular analysis ruled out the diagnosis of EATL.
2) MEITL is characterized by the expression of CD8 and CD56 in the majority of the cases. However, it has been reported that 6-13% of the cases lack CD56 expression. The lack of CD56 and/or CD8 expression should not preclude the diagnosis.
3) Around 70% of MEITL cases have a TCR gamma-delta derivation with often STAT5B mutations characteristic of gamma-delta derived T-cell lymphomas. Nevertheless, more recently, it has been described that around 63% of MEITL cases regardless of the gamma-delta or alpha-beta T-cell derivation carry mutations in STAT5B. The most commonly mutated gene is SETD2 reported in up to 85% of the cases. These two gene mutations seem to be characteristic of MEITL, and are not or only rarely present in EATL.

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T-cell lymphoma with TFH profile presenting primary in the colon

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Case description: A 76-year-old male patient with hypertension and dyslipidemia. He underwent a nefrectomy due to clear cell renal carcinoma and is currently in renal failure. He attend the clinic for diarrhea and in his analysis, a worsening of the creatinine values was observed, so he started hemodialysis without improvement of the renal function. In analytical, 2(IgG kappa and IgA lambda) monoclonal bands were observed. CT-SCAN: Splenomegaly of 15 cm and thickening of the wall of the left colon and sigma with discrete increase in mesenteric and mediastinal adenopathies, not pathological features. A colon biopsy is performed
Biopsy fixation details: Formalin fixed and paraffin embeded tissue
Frozen tissue available: No available
Details of microscopic findings: Colon biopsy with a widening of the lamina propria due to an heterogeneous proliferation of cells with histiocytic and lymphoid features and accompanying eosinophils. Lymphocytes show medium size with vesicular and irregular nuclei and nucleoli. Some larger and hyperchromatic nuclei are identified. An increased number of plasma cells is also recognized. The mucosa is not involved.
Immunophenotype: T-cell population with expression of CD3 and CD2 with loss of CD5 expression and double intensity for CD7. CD4 is positive and PD1 is weakly positive. Plasma cell population is CD138 positive and shows kappa chain restriction
Cytogenetics: No available
Molecular studies: Clonality analisis shows TCR and IgH clonal rearrangements
ISH for EBV showed some scattered positive small cells not consistent with the plasma cell population
Proposed diagnosis: T-cell lymphoma with a clonal plasma cell proliferation not associated with EBV
Interesting feature(s) of submitted case: The interest of the present case lies in the primary presentation in the digestive tract without apparent nodal involvement of an angioimmunoblastic T-cell lymphoma (AITL). Patients with AITL usually present with generalized lymphadenopathy in up to 80% of cases (1) and a constellation of characteristic symptoms associated with hypergammaglobulinemia with a very aggressive clinical course. However, some patients develop histological lesions before presenting an exuberant clinic which, as was shown in the workshop of the European congress of hematopathology (2) held in Lisbon in 2012, makes it difficult to diagnose this entity, especially in those cases in which that we cannot demonstrate loss of T antigen expression or clonality of the TCR receptor. On the other hand, it is interesting to recall the relative association of AITL with mono- or oligoclonal B proliferations or even true B-cell lymphomas, usually associated with Epstein Barr virus infection. However, these B proliferations can occur in T lymphomas without the virus RNA being demonstrated (3), and they frequently show a plasmocytoid morphology like in the present case.

1. J Clin Oncol. 2013 Jan 10;31(2):240-6. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. Federico M et al
2.Histopathology. 2014 Jan;64(2):171-99. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward - report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology.Attygalle AD et al.
3.Am J Surg Pathol. 2007 Sep;31(9):1310-22. Epstein-Barr virus negative clonal plasma cell proliferations and lymphomas in peripheral T-cell lymphomas: a phenomenon with distinctive clinicopathologic features. Balagué O et al

EAHP18-LYWS-447

Type 2 CD8 positive Refractory Coeliac disease progressing into Enteropathy Associated T-cell Lymphoma

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Case description: 43 year-old male with a diagnosis of coeliac disease since 2009 (Total villous atrophy, Antitransglutaminase antibodies, diarrhea)
Despite gluten free diet, persistence of symptoms, with important denutrition and weight loss in Autumn 2015
In January 2016, Presence of mesenteric and retroperitoneal adenopathies ; Duodenal biopsies : subtotal villous atrophy with intraepithelial lymphocytosis CD3+ CD8+. TEP CT , no signs in favor of lymphoma. Fever, night sweats and denutrition
May 2016 : TEP CT Scan : Celiac, mesenteric (SUV Max 9.5) and retroperitoneal adenopathies (SUV Max 7.3). Hypermetabolism of small intestine (SUV Max 7.2) and left colon. No hepatosplenic hypermetabolism.
Enteroscopy : pavimentous , oedematous and atrophic pattern of duodenal and jejunal mucosa. No ulceration and no stenosis. Biopsies of duodenum and jejunum
Biopsy fixation details: formalin **Frozen tissue available:** No
Details of microscopic findings: Same pattern in duodenal and jejunal biopsies.
Presence of subtotal villous atrophy with intraepithelial lymphocytosis (around 50 lymphocytes for 100 epithelial cells) and strong lymphocyte infiltration of the lamina propria
Presence of a few cluster of large cells in the lamina propria.
Immunophenotype: By immunohistochemistry, the lymphocytes express CD3, CD8, Granzyme B, CD103, NKP46 and do not express CD5. The intraepithelial lymphocytes express CD3, CD8, NKP46 and do not express CD5. A few cluster of large cells express CD30.
Interestingly, the retrospective analysis of the 2015 biopsies confirmed the presence of lymphocytes with the same phenotype without the presence of large cells CD30+ in the lamina propria.
By flow cytometry and separation of Intraepithelial lymphocytes (IEL) from lamina propria (LP) lymphocytes :
62% of IEL express CD103, are surface CD3 negative and CD8+ (SRII phenotype)
59% of LP lymphocytes have the same phenotype as IEL with granzyme B in 50%.
Presence among the blood lymphocytes of 19% of lymphocytes with SRII phenotype
Cytogenetics: No **Molecular studies:** Presence of the same predominant clonal rearrangement of TCR gamma in the 2016 duodenal, jejunal biopsies and in the blood.
Presence of a clonal TCR gamma rearrangement on the 2015 biopsy.
Proposed diagnosis: CD8+ type II refractory coeliac disease with minimal intramucosal transformation in Enteropathy associated T cell lymphoma
Interesting feature(s) of submitted case:

- Conserved CD8 expression in refractory sprue can be misleading and in there was in this case a delay for optimal diagnosis
- Interest of NKP46 staining in favor a refractory sprue type II (Morgane Cheminant et al, NKp46 is a diagnostic and prognostic biomarker and a therapeutic target in gastrointestinal T-cell lymphoproliferative diseases: a CELAC network study, submitted)
- Difficulty of assessment of transformation when presence of small clusters of CD30+ large cells but clinical presentation favors this diagnosis
- Unusual strong Lamina propria involvement for a type 2 Refractory coeliac disease.

EAHP18-LYWS-449

Gastric anaplastic large cell lymphoma, ALK-negative

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Case description:
A 66 year-old man presented in 2013 with B symptoms. CT revealed marked lymphadenopathy of the chest and abdomen with splenic lesions concerning for lymphoma. After pericardial lymph node biopsy, a diagnosis of classic Hodgkin lymphoma was rendered at another institution based on CD30 positivity without CD3 or CD30 expression. Treatment with ABVD chemotherapy regimen was initiated but discontinued during cycle 5 because of bleomycin-induced acute congestive heart failure. Serial imaging showed no disease recurrence until May 2017 when a CT revealed new gastrohepatic lymphadenopathy and a PET-avid gastric mass. The patient was transferred to our institution, and endoscopy further characterized the gastric mass as an ulcerated submucosal lesion located at the cardia. Biopsies were taken.
Biopsy fixation details: Neutral-buffered formalin
Frozen tissue available: None
Details of microscopic findings: Sections of the gastric mass demonstrate a dense infiltrate in the lamina propria and submucosa comprised predominantly of large mononuclear cells with fewer interspersed small lymphocytes. The large cells have irregular nuclear contours and prominent block-like nucleoli. Rare cells with eccentric horseshoe-shaped nuclei are identified. No 'doughnut' cells are identified.
Immunophenotype: The large neoplastic cells are positive for CD30 (membranous and Golgi-dot pattern), CD2 (dim), CD4 (dim), CD7 (subset), CD8 (subset), CD43, and CD45. They are negative for PAX5, CD15, ALK, CD56, CD5 and CD20. EBER-ISH is negative. p63 shows weak nuclear positivity in a minority of neoplastic cells.
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Anaplastic large cell lymphoma, ALK-negative, involving gastric mucosa

Interesting feature(s) of submitted case:
ALK-negative anaplastic large cell lymphoma has been recently recognized by the 2016 WHO classification as a distinct entity. ALK-negative ALCL is infrequently found in extranodal, non-cutaneous sites. Head and neck mucosal involvement has been characterized, but description of primary gastrointestinal ALCL is limited.

This case represented a diagnostic challenge given the reported history of classic Hodgkin lymphoma and a pattern of gastric mucosal involvement suggesting carcinoma. Following diagnosis of the gastric mass, retrospective analysis of the 2013 pericardial lymph node biopsy demonstrated it to be negative for PAX5 and positive for CD2, CD43, and CD45. The gastric mass therefore represents a recurrence of a previously misclassified ALK-negative ALCL, emphasizing the need for complete immunophenotypic characterization of large cell lymphomas.

The morphologic and immunophenotypic findings of ALK-negative ALCL can be used to infer cytogenetic findings and inform prognosis. Weak p63 expression in a minority of neoplastic cells suggests a lack of TP63 rearrangement. No 'doughnut cells' are identified, suggesting lack of DUSP22rearrangement. ALK-negative ALCL lacking both DUSP22 and p63 rearrangements are associated with intermediate outcomes.

EAHP18-LYWS-451

Fatal disseminated enteropathy-associated T-cell lymphoma arising from untreated celiac disease

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Case description: A 42-year-old woman was admitted with diarrhea, malnutrition, and 30 pound weight loss. Endoscopy demonstrated duodenal nodularity and ulceration. She was diagnosed with celiac disease and was positive for HLA-DQ2, but was non-adherent to a gluten-free diet. Three years after her initial presentation, she was admitted with diarrhea, anemia, and metabolic acidosis. Endoscopy showed small intestine mucosal edema and ulceration. She developed red-violaceous firm papules on her bilateral lower extremities. The patient's condition deteriorated and she expired.
Biopsy fixation details: Neutral-buffered formalin
Frozen tissue available: No
Details of microscopic findings: The initial duodenal biopsy showed villous blunting, ulceration, and an intraepithelial infiltrate of small mature lymphocytes, consistent with celiac disease. Changes indicative of enteropathy-associated T-cell lymphoma were not present.
Three years later, jejunal biopsy demonstrated focal aggregates of atypical medium to large lymphoid cells with prominent nucleoli and moderate amounts of cytoplasm in the lamina propria.
The concurrent bone marrow aspirate showed abundant medium-large lymphoid cells with irregular nuclei, prominent nucleoli, and vacuolated cytoplasm. Rare hemophagocytic histiocytes were noted. The biopsy was hypercellular (>90%) and involved by mature T-cell lymphoma (30%) with sheets of atypical lymphocytes.
A left lower leg skin punch biopsy demonstrated dermal aggregates of atypical lymphocytes with morphology similar to the bone marrow biopsy. Liver, lung, abdominal lymph nodes, and dural tissue collected at post-mortem examination showed dense infiltrates of atypical lymphocytes with the same morphologic features.
Immunophenotype: The initial duodenal biopsy revealed a population of mostly small T-cells with a majority showing expression of CD8 with aberrant loss of CD2, partial CD5, and partial CD7 expression. Flow cytometry demonstrated CD103+ T-cells; a subset were positive for CD2, dim CD3, CD7, and CD8 and negative for CD4, CD5, and TCR alpha/beta.
The jejunal biopsy showed large atypical T-cells that were positive for CD8, CD30, and CD43 by immunohistochemistry.
The atypical lymphoid infiltrate in the bone marrow was comprised of T-cells that expressed CD2 (partial), CD8, CD30 and dim CD45 and were negative for CD1a, CD3, CD5, CD7, CD56, ALK and TDT by immunohistochemistry.
Cytogenetics: 46,XX[20]

Molecular studies: T-cell gene receptor rearrangement studies of the duodenal biopsy show a distinct monoclonal peak in a polyclonal background. An identical monoclonal peak in the same position is present in the subsequent jejunal, skin, and bone marrow biopsies.

Proposed diagnosis: Fatal disseminated enteropathy-associated T-cell lymphoma arising from untreated celiac disease
Interesting feature(s) of submitted case: This case typifies the natural history of enteropathy-associated T-cell lymphoma (EATL) arising from untreated celiac disease in an HLA-DQ2 positive patient.

The initial duodenal biopsy could be classified as refractory celiac disease type 2 based on the aberrant immunophenotype and monoclonal T cell receptor gene rearrangement. The EATL immunophenotype is typical with the exception of CD8 positivity, which was also noted on the initial duodenal biopsy.

The presence of identical monoclonal T-cell receptor gene rearrangements in the initial duodenal biopsy and all subsequent biopsies indicates a clonal relationship among these lesions and provided further support for the diagnosis of lymphoma. Clonality also helped confirm the diagnosis in the jejunal sample which had a sparse neoplastic infiltrate.

EAHP18-LYWS-455

A case of primary intestinal T-cell lymphoma with unusual phenotype.

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Case description: A previously healthy 73 year-old woman was worked-up due to anemia. In her previous history there were episodes of subileus in 2016. During the autumn 2017 unclear gastrointestinal bleeding was found and in November 2017 an overt ileus developed. Imaging showed a slight thickening of part of the jejunum intestinal wall. Biopsies were taken from a tumorous area close to ligamentum Treitz. A bone marrow investigation including flow cytometry was unremarkable.
Biopsy fixation details: 4 small biopsies were provided with only sparse representation of the overlying epithelium that did not show any atypia or significant lymphocyte infiltration. In the underlying tissue there was a dense infiltrate of large atypical cells with numerous mitotic figures. Cells were pleomorphic with nucleoli but only rare cells with hallmark morphology were detected.
Frozen tissue available: not available
Details of microscopic findings: 4 small biopsies were provided with only sparse representation of the overlying epithelium that did not show any atypia or significant lymphocyte infiltration. In the underlying tissue there was a dense infiltrate of large atypical cells with numerous mitotic figures. Cells were pleomorphic with nucleoli but only rare cells with hallmark morphology were detected.
Immunophenotype: CD45+, CD3+, CD2+ (weak), CD5+, CD7+, CD4+, betaF1+, CD30+ (strong and homogeneous), granzyme B + (in few cells), BCL6+, ki-67 80%
ALK1-, CD8-, PD1-, CD56-, perforin-, p63-, p53-, B-cell markers-, cytokeratin-
Cytogenetics: not done
Molecular studies: PCR analysis of T-cell receptor gene rearrangement (Biomed2 primers) showed clonal rearrangement of T-cell receptor gamma and beta.
FISH analysis (break-apart probes) showed no rearrangement of BCL6, MYC or DUSP22-IRF4.
Proposed diagnosis: The differential diagnosis is between EATL transformed and gastrointestinal ALCL, ALK negative. The homogeneous expression of most T-cell markers is unusual in EATL. On the other hand gastrointestinal ALCL has not been reported to express betaF1. Based on the strong expression of CD30 and the lack of evidence for coeliac disease (although the overlying mucosa was sparsely represented) we favored a diagnosis of gastrointestinal ALCL, ALK negative.
Interesting feature(s) of submitted case: This is a difficult case to classify due to the unusual co-expression of most pan-T cell markers and strong expression of betaF1 and CD30 in the tumor cells.

EAHP18-LYWS-456

A case of enteropathy-associated T-cell lymphoma

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Case description: A 43-year-old female. Previous chronic stomach pain where gastroscopy with duodenal biopsies could not prove celiac disease. Seeks ER with pronounced stomach pain. Acute surgery where a 5 cm large tumor in jejunum and several enlarged lymph nodes in mesenteric fat are removed.
Biopsy fixation details: Formalin fixation of jejunum, paraffin embedded tissue sections.
Frozen tissue available: None
Details of microscopic findings: Tumor with a central ulceration, with proliferation of atypical cells of middle-sized, monomorphic lymphoid appearance, with a few dispersed larger blast cells. Atypical lymphoid cells are also seen in mesenteric lymph nodes and in one of the resection margins.
Immunophenotype: Immunohistochemical stainings in tumor sections show that the atypical lymphoid cell population express CD3, CD7 and CD8, partial expression of CD2 and CD56, and are negative for CD4 and CD5. Partially positive for the cytotoxic markers Perforin and TIA-1, negative for Granzyme B. CD30 only expressed by a few enlarged blast cells. Eighty % of the tumor cells are positive for Ki67. Negative for B cell markers CD20 and CD79A.
In resection margins: an increased amount of intraepithelial CD3 and CD8 positive lymphocytes are observed in one resection margin. In the other resection margin, shortened villi and an increased amount of atypical intraepithelial lymphoid cells that are weakly positive for CD3 and CD8 are observed.

Cytogenetics: None
Molecular studies: None
Proposed diagnosis: Enteropathy-associated T-cell lymphoma (EATL, WHO 2016).
Interesting feature(s) of submitted case: The case corresponds best with EATL, because an increased amount of intraepithelial T lymphocytes were observed in one of the resection margins. However, CD8 and CD56 positivity is more often observed in monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL, WHO 2016), which has also been considered.

EAHP18-LYWS-468

An emergency case presenting with jejunal perforation

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Case description: A 70 year-old male patient, presenting symptoms including severe abdominal pain and distension for the last three days, referred to emergency department. On physical examination generalized tenderness and defence was observed on abdominal palpation. Computed tomography revealed jejunal perforation. An emergency exploratory laparotomy was performed, revealing jejunal perforation, which prompted a resection of a segment of the affected small bowels. There was no recognizable change on his laboratory examinations based on previous medical records, except for mild lymphocytosis 9 months prior his admittance. The patient had history of hypertension and heart failure, but did not have any history of malabsorption, coeliac disease, or food intolerance, only a three-month history of diarrhoea and weight loss was obtained from his medical records. The patient was lost in intensive care unit within 6 hours of post-operative period.
Biopsy fixation details: A 23 cm segment of small intestine resection material was submitted, with a perforation area measuring 3 cm in largest diameter, 2 cm away from a surgical margin. There were no mass lesions identified on gross examination, only a dilated 6 cm segment was observed. But on cut surface, multiple fish flesh tumor masses limited to the intestinal wall was identified, some with ulcerated overlying mucosa.
The material was fixed in 10% buffered formalin for 20 hours.
Frozen tissue available: Not available
Details of microscopic findings: There was diffuse transmural neoplastic lymphoid infiltration of the intestinal mucosa, extending to seroza, distortion of villous architecture with broad expansion of villi, and prominent epitheliotropism of neoplastic lymphocytes. Tumor cells uniformly presented monomorphic medium-sized round nuclei, inconspicuous nucleoli, high mitotic and apoptotic rate, and clear cytoplasms. There was no admixed inflammatory infiltrate, nor areas of necrosis, except focal ulceration of overlying mucosa. The adjacent mucosa was heavily loaded with intraepithelial lymphocytes.
Immunophenotype: The neoplastic lymphocytes were positive for CD2, CD3, CD7, CD8, TIA1, Bcl-2, c-myc, GATA-3, and CD56; consistently negative for CD4, CD5, CD16, CD20, CD30, CD57, granzyme B, perforin, TdT, Bcl-6, MUM-1, TCR-beta-F1, ALK, and P63. CD103 was positive in neoplastic cells close to the mucosal surface, the intraepithelial lymphocytes, those infiltrating the lamina propria, and underlying the muscularis mucosa, and there was CD103 loss in the neoplastic cells close to muscularis propria. Ki67 proliferative index of neoplastic cells was 98%. The chromogenic in situ hybridization study with EBER probe revealed EBV in scarce nonneoplastic small lymphocytes and epithelial cells.
Cytogenetics: Not available
Molecular studies: Clonal T-cell receptor gene rearrangement was identified with PCR.
Proposed diagnosis: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
Interesting feature(s) of submitted case: The case without history of malabsorption or coeliac disease, presented with typical clinical, morphologic and immunophenotypical features of MEITL. There was an interesting biphasic staining pattern of CD103 on the neoplastic cells.

EAHP18-LYWS-472

Rapid Malignant Transformation of Gastrointestinal T-lymphoproliferative Disorder

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Case description: 58-year-old male with history of diarrhea for two-month duration underwent colon endoscopic biopsies. CBC: WBC 14.6 k/ul, Hemoglobin 10.8 gm/dl, platelets 299 k/ul with normal differential count and WBC morphology. His initial biopsy showed colitis with minimal intraepithelial lymphocytic infiltrates. His diarrhea persisted, later, repeat biopsies of colon and duodenum performed four months later.

Biopsy fixation details: Buffered 10% Formalin
Frozen tissue available: None
Details of microscopic findings: Patient's first set of colon biopsies (transverse and left colon) showed heavy chronic inflammatory infiltrate in the lamina propria as well as in the surface epithelium without ulceration or crypt architectural distortion. No cryptitis or crypt abscess noted. The rare lymphocytes are cytologically unremarkable and predominantly composed of CD3+ T-cells. Second and third set of biopsies (colon/rectum and duodenum) performed four months later showed dense mucosal lymphocytic infiltrate of atypical and somewhat monomorphous small to intermediate sized cells with marked epitheliotropism. The lymphocytic infiltrate also extends into the lamina propria. Duodenal mucosa additionally shows villus blunting due to the infiltrate

Immunophenotype: Immunohistochemical stains performed on the colon and duodenum (second set) showed almost all the lymphoid cells are cCD3+, CD8+, and weak CD56+. CD4 highlights scattered background small T-lymphocytes without staining in the cells of interest. Granzyme B was negative. Ki-67 demonstrates a high proliferation index at around 50-60%.
Flow cytometry analysis of the duodenal biopsy shows an aberrant population of T-cells accounting for 77% of the total cells (97% of lymphocytes) with the following immunophenotype: sCD3-, CD2+, CD4-, CD8-, CD7bright, CD16-/+, CD5-, CD25lo, CD30-, and CD103+.
Cytogenetics: Not Performed
Molecular studies: T-cell Gene Rearrangement Study: A pattern consistent with clonal T-cell receptor (both gamma and beta) genes rearrangement identified. Peaks migrating at 191 and 199 bases (Vg + Jg primer sets) on T-cell receptor gamma. In addition, a peak is present migrating at 267 bases (Vb + Jb1 primer sets) on T-cell receptor beta. The intensity of these peaks is consistent with that typically seen in clonal neoplasms.
Proposed diagnosis: Enteropathy-associated T-cell lymphoma (type 2 refractory coeliac disease > EATL, WHO 2017), aberrant T-cell phenotype
Interesting feature(s) of submitted case: The case illustrates a rapid transition from initial non-specific colitis like picture to overt Enteropathy-associated T-cell lymphoma within a span of four months. IHC stains on the initial biopsy showed rare CD3+ T-cells and negative for CD103. The later biopsies showed very distinct aberrant T-cell phenotype on Flow cytometry (surfaceCD3-, CD2+, CD4-, CD8-, CD7bright, CD16-/+, CD5-, CD25lo, CD30-, CD103+), and cytoplasmic CD3+ by IHC stains. T-cell gene rearrangement studies positive. Differential consideration include GI involvement of adult T-cell lymphoma/leukemia (ATLL) based on CD103 expression, however flow on the peripheral blood was negative for aberrant T-cell population and HTLV-1 serology was negative. The case illustrates importance of followup GI biopsies in management of refractory diarrhea cases. Ref: I Hideki et al. High expression of intestinal homing receptor CD103 in ATLL, similar to other CD8+ T-cell lymphomas. Am J. Surg. Pathol 2016;40:462-470.

EAHP18-LYWS-506

Two cases of Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma, same diagnosis with different immunoreactivities.

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Case description: 2 cases of presented with a short history of symptoms of intestinal obstruction from a 79-year-old (case 1: 1723109) and 57-year-old (case 2:1800983-referred case from other center) males. Both had their small bowels surgically resected.
Biopsy fixation details: Both resected small bowels showed, dusky appearance and covered with slough. There are 3 perforated areas seen in the bowel of case 1, that measure 50x15mm, 45x28mm and 31x12mm respectively. No perforated areas were noted in bowel case 2. Both cases have an ulcer without any other solid masses on the intestinal mucosa.
Frozen tissue available: Not done in both cases
Details of microscopic findings: Sections from the small bowel in both cases exhibit ulcerated mucosal layer, with diffuse transmural neoplastic cells infiltration. The tumour cells appear fairly monomorphic, comprise small to medium-sized having mild pleomorphic round to oval nuclei with fine granular chromatin. The nucleoli are small. Cytoplasm is clear and scanty, giving the neoplastic cells of monocytoid appearance. There are scattered reactive larger cells with vesicular nuclei, fine chromatin and small nucleoli. The cytoplasm is scanty. Mitoses are seen. The viable mucosa in both case 1 and case 2(observed in the sections from IHC slides [it is a referred case to our center]) exhibit blunting and expansion of the villi due to the tumour cells infiltration within the lamina propria.
Immunophenotype: Case 1: These cells are immunoreactive to CD3,CD8,CD7,perforin, TCR-Beta and TIA. Negative for CD20,CD2,CD4,CD5,CD56, TCR Gamma and TdT. Proliferative index is increased (50%).
Case 2: The tumour cells are CD3+, CD56+,CD7+,CD2+,CD8+ & TCR-beta+, with ki67 of 50-60%. They are CD20-,CD5-,CD30-,CKAE1/3-,CD4-,TIA-,perforin-,MPO- and TCR gamma-.
Cytogenetics: Not done in both cases
Molecular studies: Not done in both cases
Proposed diagnosis: Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma
Interesting feature(s) of submitted case: Both cases were clinically and histomorphologically fit the diagnosis of MEITL. However, they have different immunoreactivity behaviours. The first case, the tumour cells are negative to CD56 despite immunoreactive to the cytotoxic markers of TIA and perforin (we do not have granzyme B in our center). The second case, the neoplastic cells are immunoreactive to CD56 but are negative to cytotoxic markers. Both cases did not show cealiac disease changes and were immunoreactive to TCR-beta and negative to TCR-gamma. Unfortunately, we do not have MATK antibody to further support the diagnosis of MEITL.

EAHP18-LYWS-528

Type 2 Refractory Celiac Disease

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Case description: 69-year-old male patient complaining of watery diarrhea and 30 pounds weight loss over the past 1.5 years. Denies fevers, chills or night sweats. He underwent multiple colonoscopies revealing several polyps but no evidence of ulcers or masses. Biopsies showed tubular adenomas and areas suspicious for lymphocytic colitis. The most recent colon biopsy brought suspicion due to the dense lymphocytic infiltrate. Further studies demonstrated an atypical T-cell infiltrate as described below (see case below). Subsequent upper gastrointestinal endoscopy revealed diffusely erythematous gastric mucosa and multiple small non-bleeding duodenal ulcers. Biopsies demonstrated involvement by the same process (see case below). There was no evidence of masses.
CT of abdomen and pelvis revealed no evidence of organomegaly, lymphadenopathy or masses. PET-CT demonstrated only diffuse physiologyc metabolic activity. Serologic testing for celiac disease (serum IgA as well as anti-gliadin and anti-tissue transglutaminase antibodies) were negative.
Currently (1 month after upper GI biopsies) the patient remains symptomatic and unresponsive to therapy with budesonide 9 mg daily. Gluten free diet has not been attempted.
Biopsy fixation details: Formalin 10%
Frozen tissue available: Not available
Details of microscopic findings: The colonic mucosa showed preserved architecture with a dense lymphocytic infiltrate involving the lamina propria and epithelium. Lymphocytes were small to medium size with minimal atypia including irregular nuclear contours. Rare eosinophils and plasma cells were seen in the background (see images).
The duodenal mucosa showed severe blunting of the villi, crypt hyperplasia, and markedly increased intra-epithelial lymphocytes. Lymphocytes were small to medium size with mild atypia including irregular nuclear contours and nuclear clefting. Few eosinophils, plasma cells and histiocytes are seen in the background (see images).
The gastric mucosa showed foveolar hyperplasia and increased lymphocytes in the lamina propria and epithelium.
Immunophenotype: In the colonic mucosa, the lymphocytes were positive for CD2, CD3, CD4, CD7 and perforin (weak). The lymphocytes were negative for CD5, CD8 (rare positive cells), CD56, CD30, PD1, granzyme B (rare positive cells), TIA (rare positive cells), TCRBF1 and TCRdelta. Proliferation index by MIB1 (Ki-67) was approximately 10%. EB-virus encoded RNA by CISH (EBER) was negative.
In the duodenal and gastric mucosa, the lymphocytes demonstrated similar immunophenotype including positive CD3 and negative CD5, CD30 and CD56. Unlike the colonic biopsy, most of the intra-epithelial lymphocytes were CD4-/CD8-. The lymphocytes within the lamina propria were predominantly CD4+ but intensity was decreased as compared to the colonic biopsy. Proliferation index by MIB1 (Ki-67) was approximately 10%.
Cytogenetics: Not performed
Molecular studies: TCR gene rearrangement studies performed on gastric, duodenal and colonic biopsies detected the same clonal (biclonal/biallelic) population of T-lymphocytes.
Proposed diagnosis: Type 2 Refractory Celiac Disease
Interesting feature(s) of submitted case: Serologic studies for celiac disease were negative but patients who develop RCD are likely to have negative antibodies (PubMed ID: 19014942, 18996383 and 20332526).
The immunophenotype differs from the usual CD4-/CD8- or CD4-/CD8+ commonly reported for cases of type 2 celiac disease or enteropathy-associated T-cell lymphoma (EATL).
EATL was not favored due to the lack of an overtly pleomorphic lymphocytic infiltrate and the lack of large ulcers, nodules, masses, or strictures.

EAHP18-LYWS-530

Indolent T-cell Lymphoproliferative Disorder of the Gastrointestinal Tract with Regional Lymh Node Involvement.

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Case description: A 36 years-old male with malabsortion symptoms for 8 years, with suboclussive episodes and weight loss. Refractory celiac disease was suspected and treated without improvement. At 2008 a severe suboclussive episode lead to a surgical resection that included a regional lymph node. After the diagnosis the patient was treated with metothrexate for 6 months with short improvement but gastrointestinal symptoms returned. Subsequently he has received several treatments including cyclophosphamide with mild improvement. The patient is alive with persistent symptoms 8 years later.
Biopsy fixation details: Formalin fixed
Frozen tissue available: No
Details of microscopic findings: The biopsy of the small bowel showed expansion of the lamina propia by a dense, non-destructive lymphoid infiltrate involving both mucosa and submucosa with mild epitheliotropism. The infiltrate is monotonous composed of small, round and mature-appearing lymphocytes admixed with scattered inflammatory cells.
The lymph node showed a relatively preserved architecture and a lymphoid proliferation with a nodular pattern that resembled prominent primary follicles surrounded by a monotonous population of small lymphocytes.
Immunophenotype: The study of the intestinal biopsy revealed that the lymphocytes harbored a mature T-cell phenotype without phenotypic aberrancy. The infiltrate was positive for CD8 with expression of TIA-1. The staining for CD56 was negative. The EBV in situ hybridization was also negative. The proliferative index evaluated with Ki67 was low, around 5-10%.
The immunophenotypical study of the lymph node showed primary B-cell follicles surrounded by a CD8+ T-cell population.
Cytogenetics: Not done
Molecular studies: The analysis of the TCR-gamma chain rearrangement showed the same monoclonal peak in the intestinal and mesenteric lymph node. IGH rearrangement at FR3 region was polyclonal in the lymph node biopsy.
Proposed diagnosis: Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract with regional lymh node involvement.
Interesting feature(s) of submitted case: The long and chronic clinical presentation that lead to different clinical diagnosis and the lymph node involvement.

EAHP18-LYWS-545

Refractory celiac disease type 2 (RCD II) with polyclonal TCRβ gene rearrangement and STAT3 mutation

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Case description:
A 69-year-old man was referred to neurology in 2013 with a 10 year history of dystonic/myoclonic movements. Extensive workup included serologic studies, which detected anti-endomysial and anti-transglutaminase II antibodies. A small bowel biopsy reportedly showed features of celiac disease. The patient was diagnosed with central myoclonus secondary to celiac disease and was treated with antiepileptic medications, IVIG, mycophenolate, and commenced a strict gluten-free diet. In August of 2017, the neurologic symptoms worsened and the patient experienced a 40 lb. weight loss. A GI biopsy was performed to rule out a celiac-associated neoplasm, including lymphoma.

Biopsy fixation details:
Biopsies were fixed in formalin. Fresh tissue was submitted for flow cytometry and NGS studies.

Frozen tissue available: None
Details of microscopic findings:
Biopsies from the 2nd part of the duodenum showed mild crypt hyperplasia, partial villous atrophy, and marked intraepithelial lymphocytosis. The intraepithelial lymphocytes (IELs) were small and lacked cytologic atypia. No significant lymphocytic infiltrate was seen within the lamina propria.

Immunophenotype:
Aberrant IELs showed the following phenotype: CD103+, CD7(bright)+, CD2(dim)+, CD5-, CD4-, CD8-/(minor subset)+, TIA1+, Granzyme B(subset)+, Perforin-, TCRgamma-, CD30-, CD56-, CD57-, CD16-, and CD25-. By flow cytometry, the aberrant IELs represented 65% of all events and lacked s/cCD3 and TCR expression. IHC showed no definitive cytoplasmic CD3 expression (residual normal IELs were CD3+ by IHC).
Cytogenetics: None
Molecular studies:
TCRβ PCR performed with BIOMED-2 primers on DNA extracted from fresh tissue revealed polyclonal products.

Targeted sequencing of 467 cancer-associated genes revealed a single pathogenic mutation in STAT3 (NM_139276, c.1842C>G, p.S614R, variant allele frequency 15%) within a hotspot in the SH2 binding domain. This mutation has been reported in 10 cases (COSMIC database), including 9 T-cell lymphomas. Variants of uncertain significance were identified in IDH2 and KMT2D.

Proposed diagnosis:
Refractory celiac disease type 2 (RCD II) with STAT3 mutation

Interesting feature(s) of submitted case:
RCD II is characterized by a clonal proliferation of phenotypically aberrant IELs and is considered a precursor to enteropathy-associated T-cell lymphoma (EATL) in 60% of cases. Recent studies have reported derivation of RCD II from innate T/NK-like IELs, with frequent JAK1 and STAT3 mutations.

Our patient showed clinical evidence of refractory celiac disease, but the biopsy showed mild villous atrophy. Flow cytometry showed a large fraction of phenotypically aberrant IELs, however TCRβ clonality studies showed polyclonal products. Given the incongruent findings, we performed NGS studies to interrogate for a clonal genetic alteration, which revealed a STAT3 S614R hotspot mutation. STAT3 is a signal transducer and transcriptional activator in the JAK/STAT pathway which has been implicated in T-cell and NK cell lymphomas. Functional studies show SH2 domain mutations lead to constitutive STAT3 phosphorylation and increased cell proliferation.
RCD II generally (~75%) shows clonal, but non-functional, TCR gene rearrangements, with 50% demonstrating TCRβ rearrangements and the remainder TCRγ and/or TCRδ rearrangements. It has been suggested that cases lacking TCRβ gene rearrangement (immature phenotype) may be at lower risk of progression to EATL.
This case exemplifies how NGS was able to confirm RCD II in the absence of clonal TCR gene rearrangement.

EAHP18-LYWS-549

Primary gastric peripheral T-cell lymphoma "not otherwise specified"

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Case description: A 51-yrs old male Greek gynecologist with no significant medical history complaints of upper GI symptoms for one year accompanied by weight loss. Gastroscopy (September 2016) revealed a suspicious ulcerated tumor and after 2 unsuccessful rounds of gastroscopy-biopsies, the patient was diagnosed (October 2016) with gastric peripheral T-cell lymphoma (PTCL), NOS. CT-scan showed thickening of the gastric wall and some perigastric and small mesenteric nodules, all beneath the level of detection of PET, which demonstrated only avidity of the gastric lesion. The patient is negative for HTLV1, with no evidence of celiac disease. Biopsies after 6 courses of CHOEP for IE disease, showed persisting PTCL-NOS. After 2 courses of DICE biopsies showed again persisting PTCL-NOS (**submitted slides**).
Biopsy fixation details: Formalin
Frozen tissue available: No.
Details of microscopic findings: October 2016: Destructive gastric mucosal infiltrate of medium to large lymphoid cells with morphology and immunophenotype compatible with PTCL-NOS.

April 2017**:** multifocal, non-destructive, band-like atypical T-cell lymphoid infiltrate in the superficial lamina propria, with eosinophilia and moderate epitheliotropism, consistent with T-cell lymphoproliferative disease (T-LPD). Features of high-grade lymphoma were absent

August 2017 and November 2017 (after 2 DICE courses): persisting T-LPD
Immunophenotype: CD45RO+, CD2+, CD3+, CD5+, CD7+, CD8+, CD30+/-, CD103-/+, TCRbeta+, CD20-, CD4-, granzyme B-, perforin-, CD56-, TCRgamma-, ICOS-, PD-1-, CXCL13-
Cytogenetics: No
Molecular studies: October 2016: Clonality analysis for TCR gene rearrangements (multiplex PCR using Biomed-2 primers, followed by capillary electrophoresis): monoclonal rearrangement of TRG, TRB and TRD. Targeted deep sequencing of a panel of genes relevant to T-cell lymphomagenesis (CD28 DNMT3A IDH2 PLCG1 RHOA SETD2 STAT3 STAT5B TET2) showed a STAT3 mutation c.1940A>T (p.Asn647Ile).

April 2017: Clonality analysis was not informative due to insufficient quality of extracted DNA

November 2017: Molecular studies will be attempted and results will be send/presented
Proposed diagnosis: Primary gastric peripheral T-cell lymphoma "not otherwise specified"
Interesting feature(s) of submitted case: - Localized gastric presentation of PTCL-NOS is extremely rare
- After successful elimination of the tumor by chemotherapy, a multifocal atypical T-cell lymphoid infiltrate with eosinophilia and a gastritis-like distribution remained, consistent with T-LPD. In retrospect, the first biopsies (October 2016) also contain a similar infiltrate, suggesting that either the PTCL-NOS comprise higher- and lower-grade component (and is recurrent as the latter) or that the PTCL-NOS developed on a background of a preexisting and persistent T-LPD. Questions may be raised if the persistent lymphoproliferation represents a form of indolent T-LPD of the GI tract, which initially would have presented transformed to PTCL-NOS, although the degree of atypia is not characteristic of the indolent GI LPDs. This scenario remains speculative and we are not aware of similar cases described in the literature.

EAHP18-LYWS-558

An unusual case of indolent T-cell lymphoproliferative disorder of the gastrointestinal tract with nodal presentation

Elsa Poullot[*1], Adrian Ciupea[2], Laura Pelletier[3], Alina Nicolae[1], Christiane Copie-Bergman[1], Philippe Gaulard[1]
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Case description: A 73 year-old man underwent prostatectomy with regional lymphadenectomy for a prostatic adenocarcinoma. One enlarged lymph node (>10 mm in diameter) was identified. The patient had no B symptoms, nor splenomegaly, or hepatomegaly. WBC unremarkable.
Two months later, he developped gastro-intestinal hemorrhage. Endoscopy revealed ulcerative lesions in the duodeum and oesophagus. Colonoscopy showed a polype in the colon. Colic, ileal, and duodenal biopsies were performed.
Biopsy fixation details: formalin-fixed
Frozen tissue available: No
Details of microscopic findings: The lymph node showed an effacement of the architcture by a diffuse monotonous proliferation of small lymphocytes with slightly irregular nuclei and scarse cytoplasm.
Ileal and colic biospies showed a dense mucosal lymphoid infiltration with cytological features similar with those dscribed in the lymph node.
Immunophenotype: Immunophenotype was similar in LN and GI biopsie, with atypical lymphoid cells being:
- CD20+ (heterogeneous), PAX5-, CD79a-
- CD3+, CD5+, CD2+, CD7-, TCRab (BF1)+
- CD4-, CD8- ·CXCL13+, CD10+ (weak, heterogeneous)
- Perforin+, GranzymeB -, TIA1+ (weak, heterogeneous
- Ki67 <5% (both in the lymph node and digestive samples)

Cytogenetics: No
Molecular studies: -PCR for TCR gene rearrangement failed (unamplified DNA but will be repeated on another sample).
- NGS (targeted panel dedicated to PTCL) on colic biopsy: absence of mutation in TET2, DNMT3A, IDH2, RHOA, PLCG1, CD28, STAT3, STAT5B, SETD2.
- EBER ISH negative

Proposed diagnosis: Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract with nodal presentation
Interesting feature(s) of submitted case: Incindental discovery of a lymph node involvement by an indolent T-cell LPD of the gastro-intestinal tract within lymphadenectomy for prostatic adenocarcinoma. Cytology and low Ki67 proliferative rate are not consistent with a diagnosis of PTCL-NOS. GI bleeding resulted in the discovery of a T-cell LPD with multifocal involvement of the digestive tract, which most likely preceded the LN involvement. Another peculiarity of this case is aberrant expression of CD20 as well as coexistence of TFH markers (CD10 weak, CXCL13++) with the cytotoxic phenotype (Perforin+, GranzymeB-, TIAI+/-). In this case, no mutation reported in TFH-derived neoplasms (such as RHOA and epigenetic modifiers) and in cytotoxic PTCL (such as STAT3, STAT5B and SETD2) were identified.

EAHP18-LYWS-571

Enteropathy associated T-cell lymphomas, clonally related, with divergent morphology and phenotype

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Case description:
A 68-year-old male with a long-standing history (~40 years) of celiac disease developed persistent gastrointestinal symptoms despite adherence to a gluten-free diet. Endoscopy showed ulcerative jejunitis; however, jejunal biopsies (not pictured) showed no morphologic or flow cytometric evidence of refractory celiac disease-2 or lymphoma. The patient was treated with steroids with good response but within 6 months developed recurrent GI symptoms. Subsequent imaging studies showed multiple enhancing liver lesions. Liver biopsy revealed a T-cell lymphoma with anaplastic morphology. The patient was treated 6 cycles of CHOP chemotherapy and achieved clinical remission. Eight months following the liver biopsy, he presented with symptoms of small bowel obstruction. MRI enterography revealed jejunal stenosis. Biopsy of the jejunal stricture showed a T-cell lymphoma. He was treated with pralatrexate and romidepsin. He is alive, but showed evidence of disease progression at most recent follow-up.
Biopsy fixation details:
Biopsies were fixed in formalin. Fresh tissue was submitted for flow cytometry and PCR analysis. FFPE tissue was submitted for NGS analysis.
Frozen tissue available: None
Details of microscopic findings:
Liver biopsy: The biopsy showed a pleomorphic infiltrate of medium to large cells with irregular nuclei, vesicular chromatin, variably prominent nucleoli, and abundant cytoplasm (anaplastic morphology). Apoptotic debris and focal coagulative necrosis were noted.
Jejunal biopsy: The biopsy showed an expansion of lamina propria by a relatively monomorphic infiltrate of medium to large cells with vesicular chromatin, prominent eosinophilic nucleoli, and moderate amounts of pale cytoplasm. Large areas of coagulative necrosis were seen. Background mucosa showed partial villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis, consistent with celiac disease.
Immunophenotype:
Liver biopsy: Lymphoma was positive for CD7, CD30, MUM1, CD25, CD43; partially positive for CD45, CD2, CD5; and negative for CD103, CD3, CD4, CD8, TIA1, ALK1, CD56, CD20, PAX5, CD15 and EBER (ISH).
Jejunal biopsy: Lymphoma was positive for CD103, CD3, CD7, CD43, TCRγ, granzyme B, TIA1; partially positive for MUM1; and predominantly negative for CD30, CD2, CD5, CD4, CD8, CD56, CD57, CD16, CD25, perforin and EBER (ISH).
Cytogenetics: None
Molecular studies:
TCRβ PCR analysis of the liver and jejunal biopsies showed clonal rearrangements of the same size indicating clonally related lymphoid populations.
Polyclonal TCRβ products were seen on multiple prior duodenal biopsies that showed no evidence of lymphoma.
Targeted sequencing of 467 cancer-associated genes performed on the jejunal T-cell lymphoma specimen revealed pathogenic mutations in STAT3, SOCS1, TP53, ARID1A, ARID1B and CIITA.
Proposed diagnosis:
Enteropathy associated T-cell lymphomas, clonally related, with divergent morphology and phenotype, occurring in a patient with ulcerative jejunitis and refractory celiac disease type 1 (RCD I)

Interesting feature(s) of submitted case:
The clonally related EATL at the two locations showed different morphology and phenotype and developed in a patient with secondary RCD I (polyclonal IELs with a normal phenotype). The first presentation was extra-intestinal (liver) and the lymphoma exhibited anaplastic morphology, lacked CD103 expression and phenotypically resembled ALK- ALCL, which could have led to the classification of ALCL if the history of celiac disease was not known. Approximately 20% of EATLs evolving from RCD II lack CD103 expression, but this is uncommon in “de novo” EATL.

LYMPHOMA WORKSHOP SESSION 4

Gastrointestinal lymphoproliferative disorders

(B-cell)

Chairs: M. Calaminici, S. Montes-Moreno

EAHP18-LYWS-199

Duodenal-type follicular lymphoma with extensive involvement of small intestine and regional lymph nodes

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Case description: A 45 year old female patient presented herself with symptoms of abdominal occlusion in 2014. A CT scan showed obstruction of the small intestine with mesenterial lymphadenopathy.
Intraoperatively mechanical ileus due to a small intestinal invagination was diagnosed. A 6cm long jejunal segment was sent for frozen section analysis, as wells as a 18,5cm long jejunal segment and mesenterial fat tissue with macroscopic nodules for definitive histological evaluation.
Macroscopically the small intestine segments showed numerous polypoid mucosal formations.
Lymphoproliferative process was diagnosed in the frozen section analysis.
Biopsy fixation details: Fixation in 10% neutral buffered formalin.
Frozen tissue available: Yes.
Details of microscopic findings: Small intestinal sections show multiple prominent lymphoid follicles in the lamina propria. The follicles lack polarization and are almost entirely composed of small to medium sized centrocytes with only few recognizable centroblasts (up to 4 per high power field). Muscularis propria and outer layer of the intestine are not infiltrated by the lymphoproliferative process.
Mesenterial lymph nodes show an effaced architecture with nodular appearance, consisting of neoplastic follicles with similar morphological findings as described in the small intestine.
Immunophenotype: Expression of CD20, CD10 and BCL6 with coexpression of BCL2. No aberrant coexpression of CD5. Ki67 proliferation index is low (up to 20%). CD21 and CD23 highlight the dendritic cell network, in part confined to the periphery of the follicles.
FACS analysis shows a CD45+/CD19+/CD10+/CD5-/CD23- immunophenotype with kappa light chain restriction.
Cytogenetics: Not examined.
Molecular studies: t(14;18) PCR: positive, 536 bp amplification product (breakpoint MBR/JH4b).
Proposed diagnosis: Duodenal-type follicular lymphoma.
Interesting feature(s) of submitted case: This is a case of duodenal-type follicular lymphoma with extensive involvement of the small intestine (jejunum and terminal ileum) and mesenterial lymph nodes (stage IIE). The diagnosis of follicular lymphoma is straight forward, due to the typical microscopic appearance and immunophenotype. The differential diagnosis in this case is between duodenal-type follicular lymphoma (primary intestinal follicular lymphoma) and gastrointestinal involvement of classical follicular lymphoma (i.e. secondary involvement).
The staging examinations showed isolated adenopathy of mesenteric and celiac lymph nodes (CT scan) and a bone marrow examination did not show infiltration of FL. Furthermore the microscopic findings are consistent with duodenal-type FL: mucosal and submucosal neoplastic follicles composed of centrocytes with only rare centroblasts with sparing of muscularis propria and outer layers.
Duodenal-type follicular lymphoma is a variant of follicular lymphoma characterized by localized stage (usually stage IE or IIE) and excellent prognosis with low progression rate. Our patient is alive 4 years after initial diagnosis (although we have no information about underwent treatment).

EAHP18-LYWS-433

Duodenal-Type follicular lymphoma BCL2 “pseudo-negative” due to BCL2 mutation

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Case description: A 39 year-old woman, completely asymptomatic underwent a screening upper gastrointestinal endoscopy because of familiy history of duodenal carcinoma. The analysis revealed a 15-20 mm large polyp in the second part of the duodenum. A mucosectomy was performed with the presumptive diagnosis of tubular adenoma.
Biopsy fixation details: 4% buffered formalin
Frozen tissue available: not available
Details of microscopic findings: The duodenal mucosa showed a follicular lymphoid infiltrate mainly in the mucosa that only focally extended into the submucosa. The infiltrate also extended into the lamina propria. Cytologically, the lymphoid infiltrate was mainly composed of centrocytes with few scattered centroblasts characteristic of a nodal FL grade 1-2.
Immunophenotype: The lymphoid cells were positive for CD20, CD10, BCL6 but negative for BCL2 (clone 100D5). In contrast, the BCL2 E17 clone was positive indicating the presence of a BCL2 mutation. CD23 stain showed few follicular dendritic cells mainly located in the periphery of the follicles. MiB1 showed the distorted proliferation without polarization. CD3 showed the reactive T cells.
Cytogenetics: not available
Molecular studies: FISH analysis with a break-appart probe (BAP) for BCL2 showed a break in BCL2 locus indicative of a t(14;18) translocation.
BCL2 mutational analysis showed a mutation in p.P53Y, c.157_158delinsTA.
NGS mutational analysis pending.
Proposed diagnosis: Duodenal-Type follicular lymphoma BCL2 “pseudo-negative” due to BCL2 mutation
Interesting feature(s) of submitted case: 1) Duodenal-Type follicular lymphomas was recognized as a specific variant of FL in the 2016 revised WHO lymphoma classification
2) Although duodenal-type FL carries the t(14;18) chromosomal translocation, it has very low frequency of other genetic alterations, consistent with its indolent clinical course and low incidence of progression.
3) To our knowledge, BCL2 mutations in duodenal-type FL have not bee reported. BCL2 mutations in DLBCL and nodal FL are not rare, and are always associated with the t(14;18) chromosomal translocation. The mutations occur on the free loop-domain (FLD) of the BCL2 protein, where the canonical BCL2 antibody binds but outside the BH2 domain, indicative of a strong negative selection against mutations in this important functionally domain.
4) Mutations in BCL2 are indicative of clonal evolution but not necessarily of increased malignant potential. Nevertheless, the meaning and frequency of BCL2 mutations or other mutations frequently found in nodal FL are not known in duodenal-type FL, and warrants further studies.

EAHP18-LYWS-378

Duodenal follicular lymphoma: Clinical course spanning three decades

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Case description: A 54 year old man presented with retrosternal chest discomfort and severe reflux. Upper GI endoscopy demonstrated multiple small duodenal nodules. Biopsy revealed duodenal follicular lymphoma (D-FL). Staging studies including bone marrow examination were negative for involvement by lymphoma. The patient was observed with no systemic therapy.
At 222 months, the patient presented with an anterior abdominal wall mass. Imaging demonstrated retrocrural and left para-aortic lymphadenopathy, an infiltrative soft tissue mass around the mesenteric root and a soft tissue nodular density around the umbilicus. Abdominal wall mass biopsy showed follicular lymphoma (FL) Grade 1 (WHO). Staging workup revealed stage IV disease with mediastinal and bone marrow involvement.
Intermittent rituximab monotherapy was given for colonic involvement, extensive lymphadenopathy and bone marrow involvement (<5%) during a 2 year period.
Follow up with CT scan demonstrated progression of the disease with interval increase in the mesenteric mass. Therapy was changed to 6 cycles of rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP) with partial remission. The patient has remained stable without progression for the last 8 years.
Biopsy fixation details: Duodenum (A): Hollandes fixed, paraffin embedded tissue
Abdominal mass (B): Formalin fixed, paraffin embedded tissue
Frozen tissue available: No
Details of microscopic findings: Biopsy of the duodenal nodule showed dense lymphoid infiltrates in a nodular pattern, consisting predominantly of small centrocytes.
Abdominal wall mass biopsy consisted of a dense lymphoid infiltrate, consisting predominantly of small centrocytes.
Immunophenotype: Flow cytometry of the abdominal wall mass: CD19, CD20, CD10 and monotypic lambda light chains.
Immunohistochemical stains:

- Abdominal wall mass (B):
  - Positive: CD20, CD10, BCL2, BCL6
  - Negative: CD21, CD23, Activation induced cytidine deaminase (AID)(10%)*

- Duodenal mass (A):
  - Positive: CD20, CD10, BCL2, BCL6
  - Negative: CD21, CD23, Activation induced cytidine deaminase (AID)

*Takata et al suggested samples be reported as positive for AID when 20% or more cells show positivity for AID immunohistochemical stain .
Cytogenetics: 46 XY Normal male karyotype (abdominal mass)
Molecular studies: FISH: IGH/BCL2 Positive
Proposed diagnosis: Duodenal follicular lymphoma (D-FL) with subsequent systemic involvement by FL (WHO grade 1)
Interesting feature(s) of submitted case: This is a case of D-FL followed over a period of 32 years and highlights the clinical course punctuated by multiple relapses and remissions. The time to treatment required (TTR) was 222 months. His disease remained indolent with intermittent rituximab monotherapy for 60 months, after which therapy was switched to R-CVP with no progression for 8 additional years.
D-FL is a distinct variant of follicular lymphoma in the 2016 WHO classification, characterized by a distinct biological behavior and favorable clinical course. Long term follow up and data on these cases is relatively rare. D-FL show ongoing somatic hypermutation (SH) but are reported to lack AID expression. AID plays an important role in class-switch recombination and SH and it is expressed in the majority of nodal FLs. Our case lacks significant AID expression, even at the time of dissemination. This may influence relative genetic stability and the indolent, non-progressive course.

EAHP18-LYWS-204

Large B-cell lymphoma with IRF4 rearrangement

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Case description: The patient is a 40-year-old female who presented in 08/2017 with abdominal pain and diarrhea. Abdominal CT scan showed significant wall thickening of cecum. She was treated with antibiotics and steroid under the clinical impression of acute colitis. However, her symptoms did not improve so right hemicolectomy was performed in 09/2017.
Biopsy fixation details: Right hemicolectomy: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: There is an extensive atypical lymphoid infiltrate involving the full thickness of the cecal wall. It is composed of a diffuse to vaguely nodular proliferation of intermediate to large atypical lymphoid cells with round to slightly irregular nuclear contours, coarse chromatin, and moderate to ample pale cytoplasm. Some of the cells have a slightly plasmacytoid appearance.
Immunophenotype: The tumor cells of the cecal mass are positive for CD20, BCL6 (90%), and IRF4/MUM1 (90%), are suspicious for being kappa light chain restricted, have an elevated proliferation index per Ki-67 staining (90%), and are negative for CD3, CD5, CD10, CD21, CD23, CD138, BCL2 (0%), cyclinD1 and MYC (less than 10%). No underlying CD21 or CD23-positive follicular dendritic cell meshworks are appreciated.
Cytogenetics: Interphase FISH studies showed:
89 % of 100 nuclei have IRF4 rearrangement.
100 % of 100 nuclei have BCL6 rearrangement.
No rearrangement of BCL2 or MYC was observed.
Molecular studies: Not performed.
Proposed diagnosis: Large B-cell lymphoma with IRF4 rearrangement
Interesting feature(s) of submitted case: Large B-cell lymphoma with IRF4 rearrangement is rare and was newly recognized as a provisional entity in the revised 4th edition of the World Health Organization classification. Unusual features of this case include age at diagnosis (40 years; median age reported to be 12 years), anatomic site of involvement (bowel; most cases arise Waldeyer's ring, and most previously described bowel cases have arisen in pediatric patients), plasmacytoid cytologic appearance, and concurrent BCL6 rearrangement (reported to be present in 35% of cases of large B-cell lymphoma with IRF4 rearrangement).
Reference:
1. Salaverria I, Philipp C, Oschlies I, et al. Translocations activating IRF4 identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults. Blood 2011; 118(1):139-47.

EAHP18-LYWS-329

Cyclin D1-negative mantle cell lymphoma: an evasive presentation of a rare entity

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Case description:
A 45-year-old man underwent gastric biopsies for abdominal discomfort at an outside institution in 2005. A diagnosis of extranodal marginal zone lymphoma (MALT lymphoma) arising in a background of chronic H. pylori gastritis was rendered. Subsequent peripheral blood and bone marrow studies showed involvement by lymphoma. The patient was treated with antibiotics for H. pylori and achieved negative breath test results. The patient did well without further therapy until 2010 when he began to note intermittent rectal bleeding; colonoscopy revealed a 3.1 cm ulcerated rectosigmoid mass, which was biopsied and subsequently resected. The patient remained in remission until 2013, when he progressed with extensive adenopathy and peripheral blood involvement. The pathology from 2010 was re-evaluated.
Biopsy fixation details: FFPE
Frozen tissue available: No
Details of microscopic findings:
Gastric biopsy, 2005: H&E sections show gastric mucosa with a lamina propria infiltrate of small lymphocytes with condensed chromatin, irregular nuclear contours, and inconspicuous nucleoli. Neither lymphoepithelial lesions nor transformed cells are obvious. Intraluminal microorganisms consistent with H. pylori are noted.
Rectosigmoid mass, 2010: H&E sections show a vaguely nodular submucosal infiltrate of small lymphocytes with condensed chromatin, irregular nuclear contours, and inconspicuous nucleoli. Focally monocytoid cells are noted.
Immunophenotype:
Gastric biopsy, 2005: Limited immunostains show a dominant population of CD20+ CD43+ Cyclin D1- B-cells. Tandem flow cytometry performed on peripheral blood and bone marrow show IgM lambda restricted CD10- CD19+ CD20+ B-cells with equivocal expression of CD5 and CD23.
Rectosigmoid mass, 2010: Immunostains show a dominant population of CD20+ CD79a+ BCL2+ CD5- CD10- BCL6- Cyclin D1- IgD- B-cells. Follow-up immunohistochemistry (performed in 2013) was positive for SOX11.
Cytogenetics:
FISH studies (peripheral blood, 2005-2010):
Negative for: MALT I rearrangement, trisomy 12, and deletion 11q(ATM), 13q, and 17p(TP53)
Cytogenetic studies (peripheral blood, 2013):
46,XY,add(5)(p15),**t(6;14)(p21.1;q32)**,del(8)(p12),del(12)(p12),der(15)?t(3;15)(q11.2;q22)[5]/46,XY[15]
Molecular studies: None
Proposed diagnosis: Cyclin D1-negative mantle cell lymphoma
Interesting feature(s) of submitted case:
Mantle cell lymphoma (MCL) is characterized by t(11;14)(q13;q32), activating constitutive expression of Cyclin D1, a regulator of G1/S transition. A small subset of MCLs lacks t(11;14) and Cyclin D1 overexpression. Many of these cases express Cyclin D2 or D3, and can be identified by SOX11 expression.
This patient initially presented in 2005, before SOX11 immunohistochemistry was widely available. Site of involvement, morphology, and immunophenotype (including equivocal CD5 expression and Cyclin D1 negativity) favored a MALT lymphoma. A rectosigmoid mass presenting five years later was interpreted as recurrent disease.
Eight years following initial diagnosis, progressive clinical course and the cytogenetic finding of t(6;14)(p21.1;q32), likely involving Cyclin D3 [CCND3] and IGH, prompted re-evaluation of this lesion. In view of strong nuclear reactivity for SOX11, the patient's diagnosis was revised to Cyclin D1-negative MCL.
The marginal zone lymphoma-like variant of MCL is well-described, and can be misleading. Such lesions, while uncommon, are easily identified by Cyclin D1 immunohistochemistry. In the current case, lack of Cyclin D1 expression was as a further source of confusion. Ultimately, cytogenetic findings and confirmatory SOX11 staining allowed recognition of this lesion as a Cyclin D1-negative MCL.

EAHP18-LYWS-121

SENTENCE CASE: 72 year old male presenting with extranodal marginal zone B cell lymphoid proliferation of mucosa associated lymphoid tissue (MALT) in the colonic mucosa

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Case description: 72 year old male - routine follow-up for colonic polyps (last endoscopy 2011). Routine endoscopy and polypectomy.
Biopsy fixation details: 10% Neutral Buffered Formalin
Frozen tissue available: n/a
Details of microscopic findings: Sections demonstrate colonic mucosa with an underlying expansion by a dense, monomorphous lymphoid infiltrate composed of sheets of small to intermediate sized lymphocytes with course chromatin, some with irregular nuclear contours and many with a moderate amount of cytoplasm. Lymphoepithelial lesions are not seen. The infiltrate largely respects the surface epithelium. Scattered large cells are present within the infiltrate. A few intact germinal centers are noted at the mucosal surface / periphery of the infiltrate.
Immunophenotype: Positive: CD20, BLC2
Negative: CD3, CD5, CD10, CD43, BCL6, Cyclin D1

Cytogenetics: FISH: Presence of a variant translocation t(11;18) with one fusion of BIRC3 and MALT1, two signals for BIRC3 and one signal for MALT1.
ISCN Diagnosis: nuc ish (BIRC3x3,MALT1x2)(BIRC3 con MALT1x1)[200]
Molecular studies: PCR: Clonal immunoglobulin gene rearrangement
Proposed diagnosis: Extranodal marginal zone lymphoproliferative disorder of mucosa associated lymphoid tissue of the colon
Interesting feature(s) of submitted case: The patient had upper endoscopy 2 months later to follow-up on his history of H. Pylori chronic gastritis that was treated with antibiotics (2015). Although the lymphoid aggregates were not overtly diagnosable as MALT lymphoma, the same clone was present in the stomach as seen in the colon.

He was not treated (rare helicobacter organisms were thought to be present on immunohistochemistry; but stool antigen for H. pylori was negative); and has been followed for 14 months without new findings.

EAHP18-LYWS-186

Monoclonal Immunoglobulin Deposition Disease (IgM lambda) in the Small Bowel Mucosa associated with Chronic Diarrhea

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Case description: 78 year old man undergoes small bowel biopsies to evaluate chronic diarrhea of six months duration. Low grade B-cell lymphoma, lambda light chain restricted, consistent with splenic marginal zone lymphoma, was diagnosed on splenectomy 4 years prior. The bone marrow was involved by lymphoma in a nodular interstitial pattern at the time of splenectomy. Imaging studies reveal no lymphadenopathy. IgM lambda serum paraprotein is 2.3 g/dL.
Biopsy fixation details: Formalin-fixed, paraffin-embedded
Frozen tissue available: No
Details of microscopic findings: The lamina propria of the small bowel villi is distended by extracellular amorphous deposits, brightly eosinophilic on H&E stain. A Congo red stain is negative for amyloid deposition. Scattered lymphoplasmacytic aggregates are present in the deep mucosa.
Immunophenotype: By immunohistochemistry, the extracellular deposits show strong staining for lambda light chains and IgM heavy chains, and are negative with kappa light chains. CD20 positive B-cells present in the aggregates are negative for CD5, CD10, CD43, IgD and cyclin D1. The B-cells and plasma cells show restricted expression of lambda light chains and IgM heavy chains.
Cytogenetics: N/A
Molecular studies: PCR testing for MYD88 L265P alteration on the small bowel biopsy was negative.
Liquid chromatography/tandem mass spectrometry proteomic analysis of the extracellular deposits did not identify a profile consistent with amyloid fibril formation. Rather, abundant spectra associated with mu heavy chains and lambda light chains were detected.
Proposed diagnosis: Monoclonal immunoglobulin deposition disease (MIDD) involving the small bowel, secondary to low grade B-cell lymphoma (possibly splenic marginal zone lymphoma)
Interesting feature(s) of submitted case: MIDD is a rare manifestation of low grade B-cell lymphomas, and does not usually directly contribute to clinical symptoms. In this case, the extensive immunoglobulin deposition in the small bowel may be a contributing factor to the patient's chronic diarrhea. The low grade B-cell lymphoma may represent recurrent splenic marginal zone lymphoma; however, the involvement of mucosal sites, plasmacytic differentiation and IgM paraprotein greater than 2 g/dL are unusual features for that diagnosis.

EAHP18-LYWS-236

Primary-intestinal follicular lymphoma presenting as lymphomatoid polyposis coli.

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Case description: Colon biopsies were submitted to us in 2017 from a 82 yo female, with a familial history of colon adenocarcinoma.
Earlier colonoscopy was performed in 2014 showing a dolichocolon and multiple millimetric sessile polyps ("polyposis coli") as well as larger polyps.
Histopathology in 2014 was described as multiple hyperplastic polyps, as well as 1 'reactive' lymphoid polyp.
Mantle cell lymphoma was excluded with immunohistochemistry. Watchfull waiting policy.
Follow-up colonoscopy in 2015 was performed and similar macroscopy and microscopy results were reported by colleague gastro-enteropathologists: 1 hyperplastic polyp, 1 tubular adenoma (low-grade dysplasia), 1 reactive lymphoid infiltrate . Watchfull waiting policy.
Follow-up colonoscopy with multiple biopsies was performed in 2017 and submitted to our department.
Patient is asymptomatic, has no cytopenias, no lymphadenopathies.
Duodenoscopy was never performed.
Biopsy fixation details: Formalin 6%
Frozen tissue available: n/a
Details of microscopic findings: Apart from some hyperplastic polyps, the majority of colon mucosa biopsy samples showed normal epithelial glands, but the presence of prominent, vaguely nodular lymphoid infiltrate in mucosa and submucosa.
The nodular areas were composed of almost uniformly small, centrocytic cells, lacking polarisation or tingible body macrophages, and were interpreted as neoplastic follicles. The surrounding cells also infiltrated the lamina propria outside of the follicles.
Both morphology and immunophenotype were consistent with follicular lymphoma, grade 1-2.
Earlier samples (from 2014 and 2015) were revised and showed similar morphology and immunophenotype.
So diagnosis was missed for 3 years.
Immunophenotype: B-cell infiltrate:
CD20+
CD10+
Bcl2+
low Ki67 +
CyclinD1 -
LEF1 -
Follicular dendritic cells, as identified by CD21, were mainly restricted to the periphery of the follicles.
Cytogenetics: FISH: 18q21/BCL2 rearrangement +
Molecular studies: n/a
Proposed diagnosis: primary intestinal follicular lymphoma (duodenal-type), presenting as polyposis coli in a patient with concomittant hyperplastic polyps and tubular adenomas.
Interesting feature(s) of submitted case:
·Primary intestinal FL is not frequent; so can be missed by gastro-enteropathologists, particularly in patients that also have concordant epithelial polyps
·Not all lymphomatoid polyposis coli is mantle cell lymphoma, but also FL can give polyposis coli
·"Duodenal-type" FL is not restricted to the duodenum, but also occurs in large intestine: suggestion to change the name to primary intestinal-type FL, instead of duodenal-type FL? Is it advisable to perform duodenoscopy?

EAHP18-LYWS-237

Indolent Large B cell proliferation in young adult - Marginal zone lymphoma with Large B cell trasnformation

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Case description: 23 year old boy h/o Presently complains of pain abdomen, loss of apettite and loss of weight on since 3 months - h/o repeated vomiting since 3 months and low grade fever
Had severe pain one day and exploratory laparotomy with ileum resection was done in 23/09/2016 - ? MALT lymphoma and was refered to our hospital
PET Scan findings reveal; Metabolically active supra and infra diaphragmatic adenopathy and metabolically active multiple serosal lesions . No evidence of disease noted elsewhere in the scan
Dec 2016 had submandibular and preauricular adenopathy
Node Biopsied – reported as Diffuse large B cell lymphoma but reviewed in tumor board and revised to atypical large B cell proliferation
Multiple colonoscopic biopsies were labeled as reactive
Patient was investigated and found to have IgA deficiency
Nodes increased in March 2017 – repeat biopsy same picture clonality done by biomed 2 primers was negative
But patient has improved spontaneously without any steroids and is being kept under observation
New biopsy done on Sept 2017 is also labeled as DLBL but patient is being kept on follow up till 1/12/2017

Biopsy fixation details: 10% Neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: 3070 CP- duodenal biopsy showed a fairly large population of clearly atypical lymphoid cells which extended across the muscularis mucosae to the underling muscle
16904CP- Node showed loss of architecture with a dense interfollicular infiltrate of polymorphous atypical cells composed of monocytoid cells with abundant cytoplasm and few reed Sternberg like cells. Admixed were histiocytes and plasma cells
44262CP- Same histology but many more monocytoid cells seen

Immunophenotype: 3070 CP- The atypical cells were intensely CD20 positive with focal MUM1 much more than CD3 and showed a low Mib1 labeling.
16904CP- The abnormal lymphoid cells were intensely CD20 , PAX5 and Mum1 positive with Mib of 30 to 40%. CD10, bcl6 were negative. CD138 stained few plasma cells. The Reed Sternberg like cells were CD30 positive but EBVLMP1 negative
44262CP- Same histology but many more monocytoid cells seen and more CD30 positive cells were seen

Cytogenetics: not done
Molecular studies: 16904Cp and 44262cP- no evidence of IgH or TCR
Proposed diagnosis: MALT lymphoma with progression to large B cell lymphoma

Interesting feature(s) of submitted case: Lymphoproliferative disease associated with IgA deficiency in young adult
Overwhelming histology which is like a frank lymphoma but clonality is negative
Indolent course inspite of no therapy given.

EAHP18-LYWS-251

Duodenal follicular lymphoma

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Case description: A 55 year old otherwise healthy female presented with hoarseness and stridor. In the process of her evaluation for this problem, she was found to have clinical features concerning for gastroesophageal reflux and an upper gastrointestinal endoscopy was done. This showed multiple small nodules in the duodenal bulb, a 3-mm erosion in the gastric antrum and a normal esophagus. Subsequent capsule endoscopy showed mucosal changes in the proximal small bowel. PET/CT scan showed patchy areas of increased FDG uptake in the bowel, but no hepatosplenomegaly or increased uptake elsewhere. Biopsies from the duodenum and an ileal nodule were taken and described below. She denied B symptoms and had no gastrointestinal symptoms. CBC and LDH were normal. Bone marrow biopsy was negative for lymphoma.
Biopsy fixation details: Specimens were fixed in 10% neutral buffered formalin.
Frozen tissue available: Not applicable
Details of microscopic findings: Histologic sections of both specimens reveal an atypical lymphoid infiltrate involving the lamina propria of the small bowel that is predominately composed of small centrocytes admixed with rare large centroblasts (<5/high power field, on average). The infiltrate both expands the lamina propria and extends up into the tips of the small bowel villi.
Immunophenotype: CD20-positive B-cells co-express CD10, show aberrant expression of BCL2, and are associated with scattered CD21-positive follicular dendritic cell meshworks. They are negative for CD5, CD43, cyclin D1 and SOX-11. CD3 stains background small T-cells.
Helicobacter pylori IHC was negative in the stomach biopsy.
Cytogenetics: Not applicable
Molecular studies: Clonal immunoglobulin gene rearrangement molecular analysis, performed on paraffin embedded sections.
Proposed diagnosis: Duodenal-type follicular lymphoma, grade 1.
Interesting feature(s) of submitted case: This is a classic case of primary duodenal –type follicular lymphoma, which is a now a distinct entity within the WHO 2017 classification. As with many of these patients, this disease was found incidentally on workup for other issues and the patient was completely asymptomatic at diagnosis. There was no clinical or radiographic evidence of lymphoma in the mesenteric lymph nodes or other sites, in keeping with the localized nature of this distinct subtype of FL. A large-scale review of primary gastrointestinal lymphomas found that there was no adverse prognosis associated with watchful waiting in patients with duodenal FL. In keeping with this data, the decision was made for observation without treatment in this patient. She remains asymptomatic and with no disease progression at 5 months after diagnosis.
[1] Lightner AL et al. J Gastrointest Surg. 2016 Apr;20(4):827-39.

EAHP18-LYWS-304

Mantle cell lymphoma with an unusual primary presentation in the appendix

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Case description: A 70-year-old man presented with fever and mid back pain radiating to the right lower quadrant. He subsequently developed acute delirium. CT imaging revealed a thickened appendix with pericecal and mesenteric lymphadenopathy. The patient underwent emergent appendectomy.
Biopsy fixation details: Formalin-fixed, paraffin embedded.
Frozen tissue available: No.
Details of microscopic findings: H&E stained sections show appendiceal parenchyma largely effaced by a vaguely nodular infiltrate which extends into peri-appendiceal fat. The infiltrate consists predominantly of small to medium sized cells with irregular nuclei, condensed chromatin, inconspicuous nucleoli, and scant cytoplasm. Singly distributed histiocytes with pink cytoplasm are present. Focally, reactive germinal centers associated with thickened mantles are noted.
Immunophenotype: Immunohistochemical stains show that the infiltrating cells are CD20+ PAX5+ B-cells which coexpress CD5, BCL2, cyclinD1, Sox11, and IgD, and are negative for CD10, CD21, CD23, CD30, CD43, BCL6, and MUM1. The proliferative (Ki67+) index is 10%.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Mantle Cell Lymphoma.
Interesting feature(s) of submitted case: This is a histologically and immunohistochemically classic case of mantle cell lymphoma (MCL) with a most unusual presentation in the appendix. A frequent manifestation of gastrointestinal disease in MCL is lymphomatoid polyposis, in which multiple lymphoid polyps are identified throughout the intestine. Gastrointestinal involvement by MCL without the macroscopic appearance of polyposis may also be seen, and occurs as superficial ulcers, large tumor masses, and diffuse thickening of the mucosa. Lymphoma presenting as appendicitis is rare, and when it occurs it is usually due to Burkitt or large B-cell lymphoma. As rare as it is for any lymphoma to cause appendicitis, it is rarer still for MCL to be found in the appendix. There are less than 5 reported cases in the literature of mantle cell lymphoma associated with appendicitis.

EAHP18-LYWS-320

Mantle cell lymphoma, "lymphomatoid polyposis", of the colon

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Case description: The patient is a 69 year old male who underwent a screening colonscopy. Colonscopy revealed a sessile polyp, 3mm, in the cecum; 2 sessile polyps, both 3mm, in the transverse colon; and a sessile polyp, 4mm, in the sigmoid colon. Multiple small sessile, benign-appearing polyps were also noted throughout the colon. Polypectomies were performed and submitted to Pathology. The polyps were comprised of an atypical monotonous lymphoid population. The differential diagnosis includes reactive lymphoid follicles versus lymphoproliferative disorder. The immunophenotype was consistent with mantle cell lymphoma (MCL) with a low proliferation rate (5-10%). The patient was referred to Hematology/Oncology (Hem/Onc). He was otherwise asymptomatic with no B symptoms. Physical exam revealed cervical and axillary lymphadenopathy. PET CT revealed numerous hypermetabolic lymph nodes. The spleen measures 14.2 cm in greatest dimension, demonstrating diffuse increased FDG uptake. The hypermetabolic spleen and extensive diffuse adenopathy were consistent with lymphoma. A bone marrow biopsy was performed, demonstrating involvement by MCL. The patient was diagnosed with stage IV disease. His MIPI score is low, 5.69, and suggests higher likelihood of response to therapy. Given age >65, Heme/Onc recommend treatment with bendamustine/rituximab for 6 cycles rather than more aggressive therapy (such as RCHOP/RDHAP followed by auto-stem cell transplant, etc.). The patient is currently on cycle 5 of bendamustine/rituximab. His therapy was complicated by skin rash and right upper extremity superficial thrombosis, none of which required cessation of chemotherapy.
Biopsy fixation details: 10% formalin
Frozen tissue available: N/A
Details of microscopic findings: An atypical lymphoid proliferation was seen in all of the polyps, and will be described together. The polyps were comprised of monotonous appearing small-to-intermediate lymphocytes with irregular nuclei, condensed chromatin and inconspicuous nucleoli. Some of the lymphoid aggregates demonstarte the presence of germinal centers. No associated large lymphoid cell population was seen. The lymphoid proliferation appeared circumscribed, and not infiltrative. The sigmoid colon polyp also revealed the presence of a hyperplastic polyp. The bone marrow clot section show the presence of multiple nodular lymphoid aggregates, with similar monotonous appearing lymphoid cells, approximately 25%.
Immunophenotype: The atypical lymphoid cells were positive for CD20, CD5, and BCL1, and negative for CD23. The proliferation rate (Ki67) was low, 5-10%. CD23 and Ki67 highlight the presence of germinal centers. The bone marrow lymphoid aggregates were CD20 positive, coexpressing BCL1.
Cytogenetics: N/A
Molecular studies: N/A
Proposed diagnosis: Mantle cell lymphoma
Interesting feature(s) of submitted case: Extranodal involvement is frequent in MCL. Gastrointestinal (GI) involvement has been reported in 10-25% of patients, either at initial presentation or during the course of the disease. A specific process known as "lymphomatoid polyposis", in which multiple lymphoid polyps are identified in the small and large intestine, has been described. The patient may be symptomatic, presenting with abdominal pain or melena, or asymptomatic, detected during screening endoscopy. The differential diagnosis of polyposis with prominent lymphoid population includes reactive lymphoid follicles versus lymphoproliferative disorder. In summary, this case represents a classic presentation of mantle cell lymphoma at initial presentation involving the colon.

EAHP18-LYWS-362

Burkitt Lymphoma and Diffuse Large B-cell Lymphoma: a Unique Case of a Composite Lymphoma of Different Clonal Origin.

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Case description: A 72-year old male patient presented with a 3-months history of abdominal pain, stool irregularities, weight loss and night sweats. Colonoscopy was unremarkable. A palpable tumor in the right lower abdomen was found and MRI-scan was suspicious of an occult perforated diverticulum of the ileocoecal valve. Laboratory tests indicated anemia of 9.3 g/dl, increased CRP (3.8 mg/dl) and elevated LDH (620 U/l). Laparatomy revealed a tumor, infiltrating the large and small intestine, gall bladder, omentum and the liver and an en-bloc resection was performed. After diagnosis of a lymphoma, the patient received R-CHOP. Rapidly, he developed an anastomosis insufficiency with peritonitis, requiring surgery. After a short interval with overall stabilization, a third surgical intervention due to small bowel perforation because of massive tumor lysis was mandatory. 20 days after initial diagnosis, the patient died of severe sepsis as a result of peritonitis.
Biopsy fixation details: 4% neutral buffered formalin.
Frozen tissue available: No
Details of microscopic findings: Histology revealed a conglomerate tumor consisting of two morphologically distinct lymphomas in close proximity and involving the small and large intestine and the omentum. The first tumor showed the morphology of Burkitt lymphoma (BL) with a monomorphic cohesive infiltrate of small- to medium-sized blasts with intermingled macrophages, creating a starry-sky pattern. The nuclei had coarse chromatin and several small nucleoli. The second lymphoma was a diffuse large B-cell lymphoma (DLBCL) of centroblastic type with a diffuse growth of medium- to large-sized cells with irregular and sometimes lobated, vesicular nuclei and membrane-bound nucleoli.
Immunophenotype: The BL cells were positive for CD20, CD10, BCL6 and MYC and negative for BCL2. There were only few scattered T-cells (CD3+, CD5+). The Ki67 index was high (>98%). In contrast, the DLBCL cells were CD20 positive, negative for CD10 and weakly positive for BCL2. 50% of the tumor cell nuclei were variably and weakly positive for MYC. The Ki67 index was 70%.
Cytogenetics: No
Molecular studies: Using a MYC break-apart and a MYC-IGH fusion probe, a signal constellation, indicative of a t(8;14)(q24;q32) could be seen in 83% of the BL cells. In the DLBCL, 50% of the tumor cells harbored a MYC amplification, but no rearrangement was ascertained. After macrodissection of the two different tumor parts, clonality analysis using Biomed-2 IGH-A and IGH-B primers, as well as with the LymphoTrack Dx IGH FR1 assay on an IonTorrent S5-XL sequencer, revealed different amplification products in the BL and DLBCL, respectively.
Proposed diagnosis: Composite lymphoma, composed of a classical BL and a DLBCL of centroblastic type.
Interesting feature(s) of submitted case: Composite lymphomas (CL) are rare, and most of them are composed of low-grade lymphoma (LGL) components. In particular, many of them show mantle cell lymphoma (MCL) in association with chronic lymphocytic leukemia or follicular lymphoma (FL). More rarely, combinations of aggressive lymphomas and LGL have been described, especially combinations of DLBCL or – still more rarely- BL with marginal zone lymphoma, MCL, FL, but also classical Hodgkin lymphoma. A different clonal origin in CL is common. However, especially CLs with a DLBCL and a LGL part are often clonally related, indicating possible high-grade transformation. The interesting features in this case are the combination of two lymphomas in CL not hitherto described, namely BL and DLBCL, and the different clonal origin of the two tumors, pointing to an independent origin of the two neoplasms.

EAHP18-LYWS-445

Ano-rectal iatrogenic immunodeficiency-associated EBV-positive monomorphic B-cell lymphoproliferative disorder and CMV infection in a patient with Crohn's disease

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Case description: A 45 year old male patient with a past history of severe Crohn's disease presented with anal discomfort, incontinence and night sweats. His Crohn's disease had been treated with azathioprine for 8 years, followed by infliximab +/- 6-mercaptopurine for 5 years. Recto-sigmoidoscopy demonstrated a 5cm long circumferential region of ano-rectal stenosis with a focally erythematous and ulcerated mucosa. An MRI scan indicated infiltration of the both external and internal anal sphincters. Biopsy from the ano-rectal region showed an EBV-positive monomorphic B-cell (DLBCL-like) proliferation together with an associated CMV infection. PET-scan confirmed the localized character of the lesion and found no evidence of disease elsewhere. Immunosuppressive therapy was withdrawn and the patient was treated with ganciclovir and rituximab alone. The lesion regressed and after 6 months of close follow-up with repeated biopsies, the patient remains free of EBV+ lymphoproliferative disease.

Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Ano-rectal biopsies showing mucosal ulceration with granulation tissue and a patchy lymphoid infiltrate composed of medium-sized to large round to oval lymphoid cells with angulated or cleaved nuclei and one or two nucleoli. Scattered immunoblastic forms were present but no Hodgkin or Reed-Sternberg cells were seen. In addition, there was a separate population of mesenchymal and endothelial cells that showed cytomegalic features and pale nuclear inclusions.
Immunophenotype: The atypical lymphoid cells were CD20+, CD10 focally+, Bcl-6+, IRF4/MUM1+, Bcl-2 focally+, and EBER+. Occasional larger cells expressed CD30 and Ki67 showed an overall proliferation fraction of 70%. The cytomegalic cells contained CMV+ inclusions.
Cytogenetics: FISH studies showed an absence of bcl2, bcl6 and myc rearrangements.
Molecular studies: B cell clonality (monoclonal FR3)
Proposed diagnosis: Iatrogenic immunodeficiency-associated EBV+ monomorphic B-cell lymphoproliferative disorder (DLBCL-like) and CMV infection
Interesting feature(s) of submitted case: The infiltrate in this case mimics diffuse large B cell lymphoma. There is the potential differential diagnosis of EBV+ mucocutaneous ulcer. The presence of an associated CMV infection is also unusual.

LYMPHOMA WORKSHOP SESSION 5

Challenging extranodal lymphoproliferative disorders

Chairs: S. Dotlic, G. Ott

EAHP18-LYWS-356

Primary thyroid nodular lymphocyte predominant Hodgkin lymphoma

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Case description: A 49-year-old woman presented with right-sided neck pain and arm weakness. Cervical spine MRI identified a 1.9 cm hyperintense nodule in the left thyroid lobe. Ultrasound revealed a 3.2 cm spongiform nodule. Past medical history was negative for thyroid disease and TSH was normal. Gross examination of the hemithyroidectomy revealed a circumscribed 2.2 cm homogeneous tan-white multilobulated nodule with fish-flesh consistency.
Biopsy fixation details: Neutral buffered formalin
Frozen tissue available: None
Details of microscopic findings: The hemithyroidectomy demonstrates an infiltrate of mostly small mature-appearing lymphocytes. Secondary follicles are identified at the periphery of the infiltrate. In other areas, the infiltrate is comprised of ill-defined serpiginous nodules that lack germinal centers and well-defined mantle zones. Intermingled large atypical cells with large, folded or multilobed nuclei, multiple, basophilic nucleoli, and scant cytoplasm are noted both within and at the periphery of the nodules. No diffuse areas of large cells are identified.
Immunophenotype: The large atypical cells show strong homogeneous reactivity for CD45, CD20, PAX5, and BCL6 and are negative for CD15, CD30, and EBER. A subset are positive for CD10. CD21 highlights intact follicular dendritic cell meshworks. CD138+ plasma cells are polyclonal. CD3 and PD-1 highlight T-cell rosettes around the large cells. Follicles at the periphery of the lesion are negative for BCL2.
Flow cytometry demonstrates a predominance of polytypic B and T cells.
Cytogenetics: Negative for IGH/BCL2 translocation.
Molecular studies: None
Proposed diagnosis: Nodular lymphocyte predominant Hodgkin lymphoma involving thyroid
Interesting feature(s) of submitted case: Disease was limited to the thyroid by PET-CT. The patient has been treated with radiation and shows no evidence of disease at nine months of clinical follow up.
Primary thyroid lymphoma is rare, representing only 5% of thyroid malignancies and 2-7% of extranodal lymphomas, 60-70% of which are diffuse large B-cell lymphoma and extranodal MALT lymphoma. To date, only one case of primary thyroid NLPHL has been reported.
The absence of extrathyroidal NLPHL is noteworthy. Previous studies express uncertainty whether thyroid HL represents a primary event or secondary involvement by nodal or thymic HL. This case provides a clear example that the thyroid can be the primary site of involvement.
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a diagnostic challenge in the thyroid due to its rarity and superficial morphologic similarity to lymphocytic thyroiditis. The scarcity of LP cells makes the diagnosis especially challenging on FNA, frequently the initial method for obtaining diagnostic tissue. Lymphocytic thyroiditis, often presenting as hypothyroidism, is a risk factor for primary thyroid lymphoma. This patient did have a histologic background of lymphocytic thyroiditis in areas away from the dominant nodule; however, showed no evidence of autoimmune thyroiditis by clinical or laboratory methods.

EAHP18-LYWS-240

ATM- and NOTCH2-mutated, CD5- and SOX11-negative blastoid mantle cell lymphoma

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Case description: A 78-years old male patient underwent routine colonoscopy after several colonic low-grade adenomas had been removed one year before. Endoscopically, the colon caecum showed an ulcerated, voluminous and apparently aggressive tumour from which a biopsy was taken.
Furthermore, the patient had a history of a not otherwise specified high-grade sarcoma in the mediastinum, which was surgically removed in 2008.
Microscopically, the submitted sample of the colon caecum showed infiltrates of a lymphoid malignancy with highly proliferative, blastoid cells, which were strongly positive for CD20 and cyclin D1, but almost negative for SOX11 and negative for BCL2 and CD5. C-MYC expression was high. Morphologically, the differential diagnosis of a high grade B-cell lymphoma and a blastoid mantle cell lymphoma (MCL) was rendered. For that reason, supplemental molecular diagnostics were performed, including a customized lymphoma NGS panel, which uncovered mutations of the serine/threonine kinase ATM, of the NOTCH2-gene and the tumour suppressor gene TP53. As the detected mutations and particularly their co-occurrence are typically observable in MCL, this lymphoid malignancy was classified as a blastoid MCL and the patient was considered - in addition to the R-CHOP - for rituximab maintenance.
Biopsy fixation details: Formalin-fixed paraffin embedded
Frozen tissue available: none
Details of microscopic findings: The biopsies taken from the colonic mucosa show few residual colonic crypts with destructive infiltration by mature blastoid lymphocytes with high proliferative and apoptotic activity. The nuclei are irregularly formed and show dispersed chromatin and sometimes eosinophilic nucleoli.
Immunophenotype:
- positive:CD20, C-MYC, cyclin D1
- negative: BCL2, BCL6, CD3, CD5, CD10, CD11C, CD34, SOX11 and EBER
- ki67: 90%

Cytogenetics: FISH analysis indicated translocation of the CCND1 gene in 76% of the cells, but there were no C-MYC rearrangements
Molecular studies:
Customized lymphoma NGS panel (68 analyzed genes) revealed the following mutations:
ATM: p.P1797S (31%) NOTCH2: p.Y2383* (39%) TP53: p.V157G (66%)
Proposed diagnosis: CD5- and SOX11-negative, blastoid mantle cell lymphoma
Interesting feature(s) of submitted case: This case represents a blastoid (transformed) MCL with an unconventional phenotype negative for both, CD5 and SOX11, and for BCL2. These phenotypical characteristics rendered it rather difficult to categorize and therefore additional molecular diagnostics (FISH and NGS) were applied, finally allowing entity-specific designation. It is further remarkable since SOX11-negative MCL are supposed to run a more indolent clinical course, which was not the case in our patient, and mutations in the ATM and NOTCH2 gene have yet only been reported in SOX11-positive MCL, while SOX11-negative ones may acquire TP53 mutations in progression. The TP53 mutational frequency in our case was the highest, indicating that this mutation has been acquired before the other ones. Admittedly, SOX11 was weakly (diagnostically discarding) expressed in a minority of cells, suggesting that its expression may have been impaired with transformation, which would fit with all otherwise puzzling details of this unusual case. Finally, establishing the integrative entity-specific diagnosis had an immediate impact on the treatment strategy of the affected patient with additional rituximab maintenance after R-CHOP.

EAHP18-LYWS-324

Rectal tonsil: recognition of a rare reactive process (and lymphoma mimic)

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Case description: A 38-year-old woman was found to have a trans anal mass and underwent resection.
Biopsy fixation details: Formalin-fixed, paraffin embedded
Frozen tissue available: No

Details of microscopic findings: H&E sections of the 2.8 x 2.2 x 2.2 cm mass reveal an extensive submucosal lymphoid infiltrate, with unremarkable overlying anorectal mucosa. There is a nodular growth pattern with many of the nodules resembling enlarged follicles, some with an expansion of their mantle/marginal zones. A cytologically heterogeneous population of small-to-medium sized lymphoid cells is present within these expanded regions; some display monocytoid features. Scattered and mostly singly distributed larger cells are noted. The germinal centers are also expanded and show reactive features.

Immunophenotype: Immunohistochemical studies show that the bulk of the lymphocytes (~80%) are CD20+ B-cells that (apart from the germinal center B-cells) coexpress IgD, CD23 and BCL2 (variably) but are essentially negative for CD5, CD10, CD43, BCL6, CCND1, MUM1 and SOX11. Ki67 is positive in ~20% of these cells. The germinal center B-cells are CD10+ BCL6+ Ki67+ and BCL2-. CD21 and CD23 highlight expanded and somewhat irregular follicular dendritic cell meshworks, without evidence of follicular colonization. CD3, CD5 and CD43 stain the fewer T-cells (~20%) that are mostly physiologically distributed in the germinal centers, while MUM1 highlights the mostly perinodular plasma cells, that are polytypic by kappa and lambda.

Cytogenetics: Negative for trisomy 3, trisomy 12, trisomy 18 and IGH translocation
Molecular studies: PCR analysis reveals the presence of polyclonal IGH gene rearrangements only.
Proposed diagnosis: Rectal tonsil

Interesting feature(s) of submitted case: Rectal tonsils were initially described in veterinary pathology as structures composed of dense lymphoid tissue and were thought to be analogous to the bursa of Fabricius. They are not widely recognized as a distinct entity in humans, but are a useful designation for the prominent reactive lymphoid tissue that can be observed at this location, and might mimic lymphoma. Approximately 20 cases have been reported in the English literature in the past decade, with a M:F ratio of ~1:2 and age range of 1-71 years. They do not typically recur following excision; this was the case with our patient who had an unremarkable rectal biopsy during one year follow-up.

It can be difficult to distinguish rectal tonsil from lymphoma, in particular extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. The current lesion demonstrated an extragerminal center B-cell expansion, which raised the possibility of a neoplastic lymphoproliferative disorder. However, the absence of architectural effacement, cytologic monotony with atypia, and monoclonality (by IGH PCR and FISH) are features that facilitate distinguishing this as a reactive process. Rectal tonsil is an important entity to recognize, and avoid misinterpretation as lymphoma.

EAHP18-LYWS-562

Composite Extranodal Marginal Zone lymphoma of MALT-type and early phase Mantle cell lymphoma of the lung

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Case description: Clinical History: 80-year-old male, non-smoker with no significant past history. Incidental discovery of a 6cm tumor mass of the inferior right lobe of the lung in december 2017. No B symptoms.
CT-scan shows a 6 cm tumor with additional small mediastinal lymph nodes <1cm.PET-scan shows low SUV =4.
Periphal blood analysis: hemoglobin level of 12,6g/dL, with normal lymphocytes and platelet count. LDH level was normal. Bronchial endoscopy is normal.
Biopsy fixation details: formalin
Frozen tissue available: yes
Details of microscopic findings: the lung parenchyma is destroyed by a nodular and diffuse lymphoid infiltrate characterized by small lymphoid cells with round nuclei and scant cytoplasm associated with a marked plasma cell component. Residual germinal centers and lymphoepithelial lesions are observed.
Immunophenotype: CD20+ CD79a+ CD3- CD5+ heterogeneous CD10- BCL2+ IgD+ heterogeneous CD23-.
Residual germinal centers are CD10+ BCL2- with CD23+ CD21+ FDC meshwork. The plasma cell component is MUM1+, CD138+ and shows kappa light chain restriction by in situ hybridization.
Staining for cyclin D1 immunostaining highlights a rim of cyclin D1 positive SOX11 negative cells around the residual germinal centers with some extension in the interfollicular areas.
The proliferative index evaluated with Mib1/Ki67 immunostaining is < 5%. Cytokeratin immunostaining (AE1/AE3) shows lymphoepithelial lesions.
Cytogenetics: Interphase FISH for CCND1 breakapart probe is positive in the rim of cycline D1 positive cells. No rearrangement is observed with MALT1 breakapart probes.
Molecular studies: IgH rearrangement is demonstrated with no evidence of biclonality. No MYD88 mutation.
Proposed diagnosis: Composite Extranodal Marginal Zone lymphoma of MALT-type and early phase Mantle cell lymphoma of the lung
Interesting feature(s) of submitted case: This case appears at first sight on HE as a classical extranodal marginal zone lymphoma of MALT-type of the lung with plasma cell differentiation and lymphoepithelial lesions. However, the immunostaining shows expression of CD5 and Cyclin D1 immunostaining highlights an unexpected cyclin D1 + SOX11- component with CCND1 rearrangement raising the question of an additional mantle cell lymphoma component (MCL).
CD5 expression in MALT lymphoma may be observed in a small subset of MALT lymphomas and it has been proposed that CD5 expression is a marker of dissemination and bone marrow involvement.
The differential diagnosis of MCL with marginal zone differentiation is excluded considering the pattern of cyclin D1 expression and of CCND1 rearranged cells restricted to a small rim around residual germinal centres.
Early phase MCL or MCL with mantle zone growth pattern is preferred to in situ mantle cell neoplasia since cyclin D1 positive cells are not strictly restricted to the inner mantle zone of the residual germinal centres but also expand throughout the mantle zone and in the intrafollicular areas.
Composite lymphoma involving MCL is a rare event and the second component is most often follicular lymphoma, followed by CLL and Hodgkin lymphoma. Composite MCL with mantle zone growth pattern associated with extranodal marginal zone lymphoma of MALT-type of the lung has not been reported yet.

EAHP18-LYWS-190

IgG4-related, monotypic and monoclonal, plasma cell proliferation of the orbit.

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Case description: A fifty-five-year-old woman, overweight, with previous diagnosis of Hashimoto thyroiditis (in 2010), reactive follicular hyperplasia lymph adenopathy of the left axilla (in 2011), asthma and type 2 diabetes (in 2013), presented, in 2017, with bilateral enlargement of parotids and lacrimal glands with no lymph adenopathies associated.
Fragment of a "mass" at the left lacrimal gland was sent for evaluation.
Serological analysis performed in 2017 reported increased IgG immunoglobulin (1940 mg/dl, normal range: 700-1600 mg/dl) with increased IgG4 fraction (54.4% of IgG, normal range: 0.7-4.2%). No clonal component was identified by peripheral blood immunephenotyping.
After revision the lymph node dissected in 2011 showed criteria for IgG4-related follicular hyperplasia (plasma cells showed polytypic light chain expression).
Biopsy fixation details: Formalin fixed, paraffin embedded.
Frozen tissue available: None
Details of microscopic findings: The lesion of the lacrimal gland showed exclusive lymphoid tissue including secondary follicles with reactive germinal centers and conserved mantles. The interfollicular area was occupied by numerous, confluent, mature plasma cells. No residual glands could be detected in the sample,
Immunophenotype: Interfollicular plasma cells showed exclusive IgG and IgG4 expression (negative for other heavy chains: IgA, IgD and IgM). They displayed monotypic expression of lambda light chain. Some plasma cells weakly expressed CD20. No infection by HHV8 was detected by immunohistochemistry (ORF73).
Cytogenetics: Not performed
Molecular studies: B-cell receptor clonality was performed on both lymph node (2011) and lacrimal gland lesion (2017). A clonal population was identified (on FR1 and FR2) in the second sample alone.
Proposed diagnosis: Monotypic and monoclonal IgG4+/lambda+ plasma cell proliferation of the orbit.
Interesting feature(s) of submitted case: Both the nodal biopsy performed 6 years earlier and the serological studies are diagnostic for IgG4-related disease. The submitted lesion of the orbit also shows IgG4 prevalence with an additional clonal, lambda light chain expression; a clonal population confirmed also by PCR.
Clonal plasma cell proliferations raise concerns on how to classify such lesions and, in particular, a recent study by Bledsoe et al (Am J Clin Pathol 2017) distinguishes two groups "Atypical IgG4+ plasmacytic proliferations" and "IgG4+ Lymphomas and Plasma Cell neoplasms". By the authors, this is based on morphological criteria for lymphoma/plasma cell neoplasm fulfillment.

EAHP18-LYWS-473

Transient Blood Transfusion Reaction Masquerading As a Post-Transplantation Lymphoproliferative Disorder Mimicking Acute Leukemia Cutis

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Case description: A 67-year-old woman with a history of therapy-related myeloid neoplasm (TRMN)/acute myeloid leukemia secondary to prior breast cancer therapy presents with acute onset erythroderma over ~90% of her body. Eight months previously, she had an allogeneic, matched unrelated donor stem cell transplant, complicated by skin and gut graft versus host disease (GVHD). A bone marrow biopsy performed 5 days prior to presentation showed (early) recurrent TRMN .The rash was not accompanied by itching or skin pain. A punch biopsy of the right thigh was performed.
Biopsy fixation details: Formalin
Frozen tissue available: N/A
Details of microscopic findings: There is a patchy, perivascular and interstitial infiltration of large, atypical immature-appearing mononuclear cells in the reticular dermis. These cells have oval to convoluted nuclei, vesicular chromatin, occasional prominent nucleoli and abundant cytoplasm. Admixed are eosinophils and small lymphocytes. Mild epidermal acanthosis and spongiosis are present, but no epidermotropism, necrotic keratinocytes, lichenoid infiltrate, or vasculitic changes.
Immunophenotype: An initial panel showed the large atypical cells to be negative for CD34, CD117, MPO, and lysozyme. A subsequent panel showed that these cells are positive for CD2, CD3, CD4, CD5, CD30, CD43 and CD45, with Ki67 expressed by ~60%. They are negative for CD7.
Cytogenetics: N/A
Molecular studies: TRG PCR: negative for a monoclonal rearrangement.
Proposed diagnosis: “Pseudoleukemia cutis”/ “Pseudolymphoma” (atypical but reactive T-cell infiltrate, probable transfusion reaction).
Interesting feature(s) of submitted case: The clinical diagnosis for the rash was GVHD, but this was excluded histologically. Rather, in the context of the history of TRMN with early relapse, the histologic findings were concerning for leukemia cutis/extramedullary acute leukemia. However, immunohistochemistry revealed that the large atypical cells were not myeloblasts, but seemingly immunophenotypically "aberrant" (CD7 negative) CD4+ CD30+ Ki67(60%)+ T cells. Together with the cytologic features, the possibility of a cutaneous T-cell lymphoproliferative process (including a consideration of an unusual T-cell post-transplant lymphoproliferative disorder) was then entertained. However, molecular studies did not reveal a monoclonal T-cell receptor gamma chain gene rearrangement. Only subsequently was a history of a recent blood transfusion at an extramural facility obtained, and hence this rather deceptive process was interpreted to reflect an unsual transfusion reaction, with the loss of CD7, expression of CD30 and proliferative index reflecting the activated status of the T-cells. The patient had rapid (<72 hours) resolution and no recurrence of her rash, further supporting a reactive etiology.
This case highlights the potential morphologic variability of reactive T-cell infiltrates, and emphasizes the importance of clinicopathologic correlation in the diagnosis of cutaneous lymphoma and leukemia. Clinicians and pathologists must be cognizant of such reactive rashes that can mimic malevolence and even masquerade as myeloid malignancies.

EAHP18-LYWS-285

Atypical lymphoid proliferations in the skull base and skeleton of a young woman, with associated indolent immature T lymphoid proliferations and myasthenia gravis

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Case description: 2009: A 23 year old female presented with a skull base/jugular foramen mass, with associated lytic lesions in the ribs, sternum and sphenoid wing; opted for naturopathic regimens and monitoring.**2011:** She developed difficulty swallowing, vocal cord paralysis, and weakness in conjunction with a 30 lb weight loss. A ventriculoperintoeal shunt was placed and the mass (now measuring 5 cm in greatest dimension), was subsequently debulked. The pathology materials were reviewed by several institutions, but no specific diagnosis or therapeutic consensus could be reached. She was treated with two doses of cyclophosphamide starting in 2012.**2014:** She suffered acute decompensation with proximal extremity weakness, diplopia and difficulty with respiratory secretions. Additional testing established a diagnosis of myasthenia gravis (MG). She was treated with pyridostigmine and prednisone, but progressed to a myasthenic crisis, evolving to respiratory failure. The skull base mass and lytic lesions remained stable, and it was unclear if her progressive symptoms were attributable to the mass itself, the MG, or both. She was given dexamethasone, IVIG and the pyridostigmine was increased. In addition, an external ventricular drain was placed and the tumor was debulked.**2016:** She presented with femoral fracture. Since then, the patient has remained stable with ongoing therapies including prednisone, rituximab, pyridostigmine, and pralatrexate (at various time points) for her MG.
Biopsy fixation details: Formalin
Frozen tissue available: N/A
Details of microscopic findings: Skull base mass (biopsied 2011, 2104), L4 bone lesion (late 2011) and femoral curettage (2016): Diffuse infiltrate of small, mature lymphocytes (some with irregular nuclear contours) with occasional small foci of larger, transformed cells with the appearance of compressed germinal centers. Scattered plasma cells and histiocytes. Rare vessels with small lymphoid cells within the walls (T cells). No necrosis. Foci of mild fibrosclerosis. An iliac crest marrow biopsy from 2011 was morphologically unremarkable.
Immunophenotype: No abnormal B cells or abnormal mature T cells by flow cytometry or immunohistochemistry (IHC). All infiltrates were composed predominantly of T cells with smaller numbers of B cells (often in aggregates) and scattered plasma cells (very focally exhibiting lambda predominance or restriction). A small (<1%) immature T cell population was identified in L4 lytic lesion and 2014 skull base mass, positive for CD1a, CD4, CD5 (slightly decreased), CD8 and TDT with variable surface CD3 and decreased CD7. A similar population was identified by IHC in the femoral curettage from July 2016.
Cytogenetics: Bone marrow and L4 lytic lesion: 46,XX[20].
Molecular studies: 2011 Skull base mass: Polyclonal B and T cells.**2011** Bone marrow (morphologically unremarkable): Clonal T cells in a polyclonal background; No clonal B cells.**2012** Peripheral blood: Same clonal T cells (as marrow) in a polyclonal background; No clonal B cells.**2014** Skull base mass: Polyclonal B and T cells**. 2014** UW Oncoplex (skull base mass): No actionable mutations, gene amplifications, or gene fusions were detected in a broad panel. **2014** Peripheral blood: Polyclonal T cells**. 2016** Femoral curettage: B cell clone; polyclonal T cells.
Proposed diagnosis: Atypical lymphoid proliferations, T cell predominant, with associated low-level indolent immature T lymphoid proliferations and myasthenia gravis
Interesting feature(s) of submitted case: Multifocal compressive or destructive atypical lymphoid proliferations with scattered immature T cells over a a prolonged time course without a specific diagnosis associated with MG.

EAHP18-LYWS-382

PICALM-MLL10 fusion linking immunophenotypically divergent acute leukemia involving bilateral skin lesions without marrow involvement.

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Case description: 42-year-old woman presented with multiple skin lesions over her torso and extremities, including a 5cm lesion on her right arm. After one month of topical steroids led to no improvement, an outside biopsy of a right-sided (R) lesion was reported as acute myeloid leukemia (AML). CBC was unremarkable and she had no systemic symptoms. PET revealed many FDG-avid cutaneous/ subcutaneous lesions. Biopsy of a left-sided (L) lesion suggested a T- lymphoblastic leukemia/ lymphoma and the discrepancy triggered an extensive work-up of both lesions. Bone marrow (BM) showed no involvement; however CSF showed abnormal blasts. She was treated with the ALL-2 regimen(cytarabine and mitoxantrone), intrathecal chemotherapy, and an allogeneic stem cell transplant (SCT). She is now 1.5 months status post-SCT with no disease.
Biopsy fixation details: Fresh, for flow cytometry, and formalin fixed bilateral skin biopsies were routinely processed. BM biopsy was fixed in formalin, followed by routine processing after decalcification. **Frozen tissue available:** na
Details of microscopic findings: Histologic sections of bilateral skin biopsies showed a similar atypical dermal infiltrate present in sheets, composed of medium to large blasts with irregular nuclei, fine chromatin, and scant cytoplasm, which did not involve the epidermis. The R biopsy showed significant crush artifact. BM biopsy showed a mildly hypercellular marrow (60%) with maturing trilineage hematopoiesis, and without increased blasts.
Immunophenotype: Blasts of the L lesion expressed CD34, CD3(weak), CD56, TdT(weak), CD79a, LMO2, CD33, CD5, CD7(strong), CD4(weak), and were negative for CD117, CD2, CD8, CD20, CD10, CD22, CD19, PAX5, CD13, CD163, CD68(KP1 & PGM1), myeloperoxidase(MPO), lysozyme, TCL1A, CD123. Ki67 index was ~ 70%. Blasts on the R were distinctive for MPO expression, in addition to positivity for CD34, CD56, CD4, CD7(strong), LMO2, and CD33, while being negative for CD3, CD117, TdT, CD5, CD2, CD8, and PAX-5. By flow cytometry, key differences included L blasts expressing cyCD3, cyCD79a, with CD5 (dim), and conversely, R blasts expressed MPO, CD15 (subset), HLA-DR (variable), and CD64 (see table for complete comparison). Flow cytometry showed blasts with a similar immunophenotype in CSF, but not in the BM aspirate.
Cytogenetics: BM karyotype showed inv(9), in all 20 metaphase cells, a known polymorphism.
Molecular studies: NGS – based RNA-fusion panel (targeting 199 genes) revealed a PICALM-MLLT10 in-frame fusion common to both skin specimens. NGS-based 400 gene somatic mutational panel (using a matched normal to exclude germline variants) identified common mutations in: ETV6, HIST1H3B, PHF6, and WT1 in addition to other unique and common events. No variants were detected in the BM.
Proposed diagnosis: Mixed phenotype acute leukemia (MPAL), T/ myeloid with a PICALM-MLLT10 fusion.
Interesting feature(s) of submitted case: This case represents a blastic proliferation limited to skin and CSF and exclusive of BM. The immunoprofile of two skin sites, left and right, showed distinct profiles which in isolation would be characteristic for early T-cell precursor acute lymphoblastic leukemia/ lymphoma (ETP-ALL) and AML, respectively. However, in light of their common morphologic and immunophenotypic features, supported by similar molecular findings, this blastic proliferation represents the same disease process and is overall in keeping with a mixed phenotype acute leukemia (MPAL), T/ myeloid. The case is also unique due to a PICALM-MLLT10 in-frame fusion, which, while is found in 10% of T-ALL cases, and can occur in AML, has only rarely been described in cases of MPAL.

EAHP18-LYWS-504

Primary Omental Gamma-Delta T-Cell Lymphoma Associated with a Clonal Hypereosinophilic Disorder and Harboring Pathogenic Mutations in FAS and SH2B3 Genes

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Case description: A 53-year-old Pakistani female had >!00 K/µl eosinophils in her blood when she presented with a 2-week history of left upper quadrant pain and lethargy. Physical examination did not show organomegaly, other masses or enlarged lymph nodes. ENT exam was normal. CT scan of chest/abdomen/pelvis showed only a huge omental cake, a small ascites, a tiny left tubo-ovarian mass. Stool was negative for parasites. Bone marrow showed 100% cellularity with only marked increase in eosinophils and eosinophil precursors. Extensive molecular and cytogenetic analysis along with flow cytometry of the marrow were negative for a clonal disorder. Idiopathic hypereosinophilic syndrome was diagnosed and an omental biopsy was advised. Hydroxyurea brought eosinophil count down to about 50K/ul. Serum CA125 was high at 368 U/ml. A clinical diagnosis of metastatic ovarian carcinoma was assumed and omentectomy, hysterectomy with bilateral salpingoophrectomy, lymphadenectomy, and multiple biopsies of small colonic serosal lesions were done without a pre-operative or intraoperative biopsy. There were no gross lesions in the uterus/bilateral adenexae at the time of frozen section (FS), which was done after the surgery to select tissue for chemotherapeutic drug sensitivity testing. A FS diagnosis of a large cell lymphoma was made. Tissue was submitted for flow cytometry and cytogenetic analysis. A diagnosis of primary omental gamma-delta T-cell lymphoma was made and she was treated with high dose methotrexate and cytoxan with leucovorin rescue. After completing chemotherapy, she was admitted with progressive weakness. CT scan of head showed multiple brain lesions. CT scan of chest/abdomen/pelvis was normal. Radiotherapy was given to the brain. A few weeks later she was admitted to the hospital with progressively increasing respiratory difficulty, developed DIC and possible Budd-Chiari syndrome, her condition deteriorated, and she died.
Biopsy fixation details: 10% Neutral Buffered Formalin
Frozen tissue available: No
Details of microscopic findings: Peripheral blood: Marked eosinophilia; Bone marrow: ~100% cellular with marked increase in eosinophils and eosinophil precursors; Omentum: Diffuse large lymphoid cell and eosinophil infiltrate with angiocentricity and large areas of necrosis; Left fallopian tube/left ovary and Tiny foci on serosa of abdominal and pelvic organs: Focal large lymphoid cell and eosinophil infiltrate; Lymph nodes: No involvement.
Immunophenotype: Immunohistochemistry: CD2-/CD3+/CD4-/CD5-/CD7+/CD8-/CD30+(focal)/CD43+/TCR gamma-delta+/ TIA-1+/granzyme+/perforin+/TdT-/Ki67+ (~100%)/CD20-/CD10-; **EBER by ISH** was negative;
Flow cytometric analysis: Poor cell viability; no lymphoma
Cytogenetics: Normal female karyotype
Molecular studies: TCR gamma gene rearrangement detected; No TCR beta gene rearrangement; **Next-Generation Sequencing using 128-gene panel:** Pathogenic mutations are detected in FAS gene and SH2B3 Mutations of uncertain significance are detected in HIST1H1E and MYCN NF1 genes
Proposed diagnosis: Primary Omental Gamma-Delta T-Cell Lymphoma Associated with a Clonal Hypereosinophilic Disorder and Harboring Pathogenic Mutations in FAS and SH2B3 genes
Interesting feature(s) of submitted case: Association of eosinophilia with peripheral T-cell lymphoma; Presentation as a clonal hypereosinophilic disorder harboring SH2B3 mutation; It is most likely a primary omental lymphoma because the most of the lymphoma is present in the omentum; Detection of FAS mutation because FAS mutations have been detected in NK/T-cell lymphomas; Overconfidence on clinical findings (anchoring bias) lead to a wrong clinical diagnosis and wrong treatment

EAHP18-LYWS-140

An Unusual "Hepatitis"

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Case description: A 23 year old female patient presented to her GP in May 2016 with a history of fever, muscle pain, fatigue, drenching night sweats and sore throat. In Feb 2017 she was evaluated for right upper abdominal pain and transaminitis; no cause was found. 'Hepatitis' was reported in March 2017 and a trial of steroids for presumed autoimmune hepatitis was started. In the absence of relief, the patient was evaluated by haematology, gastro-enterology, infectious diseases and respiratory medicine between May and October 2017. Liver biopsy was repeated in November 2017. No definitive treatment has been offered as yet; she remains under the care of hepatology and haematology.
Biopsy fixation details: 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: The liver biopsy showed mild to moderate portal tract and prominent sinusoidal inflammation. Spotty liver cell necrosis was present. The lymphoid cells were small with minimal atypia. There was no autoimmune or interface hepatitis, ductopenia or granulomatous inflammation.
Immunophenotype: Few or no B-cells were seen. The sinusoidal cells were EBV -RNA positive NK/T cells (CD56, CD2, CD3, CD16, TIA1, granzyme B positive; CD57, CD4 and CD8 negative) with a low proliferation index.
Cytogenetics: Not done
Molecular studies: BIOMED2- polyclonal Ig and TCR
Proposed diagnosis: Systemic chronic active EBV infection, NK/T cell phenotype
Interesting feature(s) of submitted case: Systemic chronic active EBV infection, NK/T-cell phenotype presenting in an immunocompetent Caucasian female

EAHP18-LYWS-145

Classical Hodgkin Lymphoma Arising in a Patient with Chronic Lymphocytic Leukemia (Richter Syndrome)

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Case description: A 66 year old man was diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in 2006 and observed until 2011. He was then treated with fludarabine/cyclophosphamide/rituximab followed by ibrutinib/venetoclax without complete remission. In 2017, an abdominal CT scan showed increasing hepatosplenomegaly and multicompartmental lymphadenopathy.
Biopsy fixation details: The tissue was fixed using formalin and submitted for morphologic evaluation and immunohistochemical studies. Flow cytometry immunophenotypic studies were performed on fresh material prepared from a concurrently collected fine-needle aspiration specimen.
Frozen tissue available: No
Details of microscopic findings: A right axillary lymph node biopsy showed a proliferation of large cells with multilobated nuclei resembling Reed-Sternberg cells in a background of small to medium sized lymphocytes, numerous histiocytes and few eosinophils. Scattered mitosis and apoptotic bodies were present. There was no necrosis.
The bone marrow biopsy showed morphologic findings. Large lymphohistiocytic infiltrates occupying approximately 20-30% of bone marrow medullary space were identified, containing mononucleated Hodgkin cells and classical Reed-Sternberg cells. Numerous small lymphocytes, histiocytes, and occasional eosinophils were present in the background.
Immunophenotype: Immunohistochemical stains were performed on both the lymph node biopsy and bone marrow core biopsy, with similar findings.
The large neoplastic cells were positive for CD30, CD15 (subset), p53 (weak) and positive for EBER by in situ hybridization. A dual-color PAX5/CD5 stain showed that the large neoplastic cells are weakly positive for PAX5 and negative for CD5. The majority of large cells were also negative for CD20. Ki67 proliferation index was 20-30%. Dual-color PAX5/CD5 stains also shows that the scattered occasional small cells have a CLL phenotype co-expressing PAX5 and CD5. The majority of the small lymphocytes in the background were CD5 positive T cells. Immunostaining was also performed for LEF-1, which showed positive staining in both the HRS cells and the small CLL cells.
Flow cytometry immunophenotyping was also performed on both the fine needle aspirations and the bone marrow aspiration. In the fine needle aspirate, analysis showed a minute abnormal lambda restricted B-cell population (1.2% of lymphocytes, 0.2% of total), expressing CD5, CD19, CD20 (dim), CD38, and CD79b and negative for FMC7. Flow cytometric analysis of the bone marrow aspirate showed the CLL cells to represent 0.01% of total cells analyzed with a similar immunophenotype. The neoplastic HRS were not detected in either flow cytometry analysis.
Cytogenetics: 46,XY[20]
Molecular studies: Not Applicable.
Proposed diagnosis: Epstein Barr virus positive classical Hodgkin lymphoma arising from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter syndrome).
Interesting feature(s) of submitted case: Progression to a more aggressive neoplasm, typically diffuse large B-cell lymphoma, occurs in approximately 5% of patients with CLL/SLL; however, about 0.4% of patients develop classical Hodgkin lymphoma. Treatment with fludarabine impairs immunosurveillance via T-cell toxicity, increasing susceptibility to EBV reactivation and may promote progression. Because the clonal relationship between CLL/SLL and second neoplasm remains unclear, many authors advocate the term Richter “syndrome” instead of “transformation.” However, the LEF-1 expression (which is regarded as highly specific for CLL/SLL) by Hodgkin and Reed-Sternberg cells in our case suggests true transformation.

EAHP18-LYWS-159

Indolent T-cell lymphoproliferative disorder of the kidney with aberrant expression of S100 and CD56

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Case description: A 67-year-old woman with a medical history of poliomyelitis and breast cancer presented with renal colic and gross hematuria. Computed tomography revealed a renal mass, located in the lower pole of the left kidney. The patient underwent transabdominal nephrectomy. Grossly, the tumor measured 9.6 cm in the greatest diameter. Histological examination was consistent with a T-cell lymphoproliferative disorder S100+/CD56+. Blood investigations were unremarkable. Bone marrow biopsy and whole body PET scan (performed 4 weeks after surgery) were both negative. After 3 cycles of CHOEP there was no evidence of disease, and the therapy was discontinued; the patient is still alive and in complete remission (follow up: 18 months).
Biopsy fixation details: The tissue was fixed in 10% neutral buffered formalin.
Frozen tissue available: No.
Details of microscopic findings: The renal structure was effaced by a monotonous proliferation of medium-sized atypical lymphocytes, with plasmacytoid appearance and interstitial-to-diffuse growth pattern; the cells had oval nuclei, inconspicuous nucleoli, coarsely clumped chromatin and an abundant rim of pale cytoplasm. A small angiomyolipoma was detected in one of the renal specimens.
Immunophenotype: The neoplastic lymphoid cells showed a non-activated cytotoxic T-cell phenotype, being diffusely positive for CD3, CD2, and Tia1, with partial expression for CD5, and CD7 loss. They also expressed S100 and CD56, and TCR βF1; tumor cells were negative for CD4, CD8, CD30, FOXP3, PD1, TCL1, CD27, perforin, granzyme B, langerin, CD1a, CD57, SOX10, HMB45 and pan-cytokeratin. Ki67 index was approximately 35%. CD20 highlighted regressed B-cell follicles, surrounded by scattered plasma cells with lambda light chain restriction. HHV-8 and CMV stains were negative, as well as in situ hybridization for EBV-encoded small RNA. Angiomyolipoma cells co-expressed Mart1/Melan-A and smooth muscle actin.
Cytogenetics: Not performed.
Molecular studies: Clonal TGR gene rearrangement was detected by PCR, performed according to BIOMED-2 protocol. Targeted next generation sequencing is pending.
Proposed diagnosis: Renal cytotoxic T-cell lymphoproliferative disorder with aberrant expression of S100 and CD56 and indolent behavior.
Interesting feature(s) of submitted case: Few cases of S100+ T-cell neoplasm have been reported in the literature: in a small series described by Hanson et al, the neoplastic phenotype was very similar to our case (S100+/CD56+/βF1+ and CD4/CD8 double-negative T-cells), but the clinical picture was quite different: Hanson's cases were characterized by leukemic presentation, hepatosplenomegaly, and an aggressive behaviour. Conversely, the present lesion shared several features with T-cell lymphoproliferative disorders (T-LPDs) of the gastrointestinal tract and cutaneous acral sites: in fact, the neoplasm showed isolated extranodal localization and an unexpected indolent clinical course, despite the worrisome morphology; moreover, atypical T-cells had a nonepitheliotropic growth pattern and non-activated cytotoxic phenotype.
As suggested for gastrointestinal and acral T-LPDs, our neoplastic cells may have arisen from tissue-resident memory T-cells: this cytotoxic T-cell subset displays homing receptors for extranodal tissue, including kidney, and can acquire the expression of S100 or NK cell markers, like CD56, with chronic immune activation.

EAHP18-LYWS-182

IgG4-related sclerosing mastitis mimicking lymphoma

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Case description: A 53 year-old woman with diabetes mellitus and hypertension presented with painless left breast lump in Jan 2017. In 2003, she was diagnosed with small B cell lymphoma (small lymphocytic lymphoma) of the left breast and was treated with chemotherapy and radiotherapy. She remained well and was lost to follow up after 2006. PET CT (Jan 2017) showed diffusely increased FDG uptake in both breasts (SUVmax 4.5). Mildly FDG-avid lymph nodes were seen in cervical, axilla and subpectoral regions (SUVmax 3.7). Bone marrow aspirate/biopsy and flow cytometry were negative for malignancy. LDH was normal. A right and left breast core biopsy revealed an atypical small B cell lymphoid infiltrate and marked stromal fibrosis. The right breast lump was excised in March 2017 for further workup. In Sept 2017, she developed right eyelid swelling and CT orbits showed enlargement of the lacrimal gland with soft tissue swelling. A right lacrimal gland biopsy was performed. Serum IgG4 was 590.0 mg/dL (2.4 - 121.0). Serum total IgG was 1740 mg/dL (767 – 1590)
Biopsy fixation details: Specimens were fixed in 10% neutral buffered formalin.
Frozen tissue available: Nil
Details of microscopic findings:
Right breast lump core biopsy (1): Dense and patchy lymphoplasmacytic infiltrate associated with reactive lymphoid follicles. The lymphocytes were small with no significant atypia. There were abundant mature plasma cells. The stroma is densely hyalinised and sclerotic.
Right breast lump excision biopsy (2) (submitted for workshop): A piece of fibroadipose tissue measuring 4.1 x 1.8 x 1.1 cm was removed and showed a mass forming lesion characterized by a prominent lymphoplasmacytic infiltrate, similar to the breast core biopsy. There were aggregates of small lymphoid cells without significant atypia and reactive follicles. Sheets of mature plasma cells were seen. The stroma is densely sclerotic.
No obvious obliterative phlebitis present.
Right lacimal gland biopsy (3): A moderately dense lymphoid infiltrate associated with reactive follicles containing hyperplastic germinal centres. Aggregates of mature plasma cells were present. There was stromal fibrosis but no obliterative phlebitis.
Immunophenotype: The predominant lymphoid cells in all the breast biopsies were small B cells, which were positive for CD20, CD79A, BCL2 and CD23. They were negative for CD10, CD5, cyclinD1, SOX11 and LEF1. Ki67 proliferation index was low. There is increased number of IgG4+ plasma cells with more than 100 per high power fields and an IgG4/IgG ratio exceeding 40%. The plasma cells were polytypic for kappa and lambda. The lacrimal gland showed similar findings. Flow cytometry of the lacrimal gland tissue showed non-clonal lymphoid proliferation.
Cytogenetics: Karyotype of bone marrow aspirate showed normal 46,XX [20].
Molecular studies: IgH / IgK gene rearrangement was performed on the right breast lump excision biopsy and results showed polyclonal rearrangement.
Proposed diagnosis: IgG4-related disease of bilateral breasts (IgG4-related sclerosing mastitis) and lacrimal gland.
Interesting feature(s) of submitted case: This is an unusual case of IgG4-related disease manifesting as bilateral breast lumps and mimicking small B cell lymphoma. The breast involvement was evident only after the diagnosis was made in the lacrimal gland. IgG4-related sclerosing mastitis is uncommon with only a few cases reported in the literature. Characteristic storiform fibrosis and obliterative phlebitis may not be present. A high index of suspicion is necessary for an accurate diagnosis and to avoid misdiagnosis of lymphoma.

EAHP18-LYWS-192

Primary nasopharyngeal lymphocyte-rich classical Hodgkin Lymphoma

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Case description: The patient was a 43 year old white Caucasian male, who had been suffering from blocked nose for 2 years, which did not improve by surgical intervention (no biopsy taken). He had no 'B' symptoms and his only co-morbidity was hypercholesterolaemia. CT scan and MRI performed to define the lesion confirmed nasopharyngeal disease only with no extension outside. An excisional biopsy of the nasopharyngeal mass was performed and a staging PET scan was undertaken following the diagnosis. PET scan demonstrated a 2 cm maximum diameter nasopharyngeal mass with some uptake in the tonsils. No lymph node disease was noted nor any other lesion identified clinically or on PET. He received 2 cycles of ABVD (Adriamycin, Bleomycin, Vinblastine and Decarbazine), followed by local radiotherapy. Repeat PET scan post 2 cycles of ABVD showed complete metabolic response and he was in complete remission 22 months after the diagnosis.
Biopsy fixation details: 10% buffered formaldehyde
Frozen tissue available: No
Details of microscopic findings: The overlying squamous and respiratory epithelium shows no significant pathology. The underlying stroma shows a vaguely nodular lymphoid infiltrate comprising very predominantly of small lymphoid cells without a significant number of neutrophils or plasma cells. Only scanty eosinophils are noted at the periphery of nodules. Amongst the lymphoid cells are scattered large polylobated LP type cells and very occasional Hodgkin Reed Sternberg (HRS)-like cells with prominent nucleoli. Very occasional residual reactive lymphoid germinal centres are noted focally.
Immunophenotype: LP and HRS cells:
CD30+, CD15+, Mum1+, Pax5+ (weak), Ki67 +,
Alk1-, CD45 (LCA)-, CD20-, CD79a-, CD3-, CD5-, CD43-, Oct2-, Bob1-, BCL6-, EBV (EBER-ISH)-.
Background lymphoid cells:
Predominantly CD20+, CD79a+ B-cells.
CD21+, CD23+ expanded follicular dendritic cell (FDC) meshwork in the nodules with very occasional residual compact FDC meshwork.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Primary nasopharyngeal lymphocyte-rich classical Hodgkin Lymphoma
Interesting feature(s) of submitted case: A very rare example of 'Primary nasopharyngeal lymphocyte-rich classical Hodgkin Lymphoma', EBV-ve, stage IE. Although lymphomas are the second commonest malignant neoplasm in the head and neck region after squamous cell carcinoma, primary nasopharyngeal classical Hodgkin Lymphomas without nodal involvement are very rare. Previous reviews suggested that they present as isolated nasopharyngeal mass, stage I or II and have a good prognosis with complete remission in patients with localized disease. The commonest subtype described is 'mixed cellularity' although one study found 'lymphocyte-rich' subtype to be the commonest.

EAHP18-LYWS-193

Crystal storing histiocytosis presenting as an ovarian mass and obscuring marginal zone lymphoma

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Case description: A 51-year-old female presented with an ovarian mass. Following hysterectomy and oophorectomy, an extensive histiocytic infiltrate was noted in the ovary, myometrium, and endometrium. No further treatment was given following surgical resection. The patient did well until 2015 when she developed generalized lymphadenopathy, lung nodules and bilateral leg plaques diagnosed as lobular panniculitis.
A transbronchial biopsy performed in 2016 showed bronchial mucosa with a non-specific lymphoplasmacytic infiltrate.
In 2017, the patient developed a left breast mass (10 x 7 cm) and a left cervical soft tissue mass. Biopsies of both lesions showed a histiocytic infiltrate, similar to that seen in the ovary, but atypical lymphoid cells were noted. A bone marrow showed no evidence of disease.
Biopsy fixation details: Neutral buffered formalin
Frozen tissue available: no
Details of microscopic findings: Sections of the ovarian mass from 2012 showed a dense histiocytic infiltrate with interspersed aggregates of lymphocytes and plasma cells. The histiocytes had abundant eosinophilic cytoplasm and containing refractile crystalline inclusions with a granular quality. A similar histiocytic infiltrate was seen in the subsequent neck mass in 2017. The breast biopsy showed a greater lymphoid component, with many of the cells containing Dutcher body type inclusions.
Immunophenotype: The histiocytes were positive for CD68, CD163 and negative for S100. The lymphoid cells showed monotypic expression of IgM Lambda, and were positive for MUM1/IRF4. Most of the lymphoid cells were positive for CD20 and BCL2. CD5, CD10 and BCL6 were negative. CD30 was negative. Ki-67 showed a low proliferation rate.
Cytogenetics: Not done
Molecular studies: PCR studies were performed on the ovarian tumor from 2012 and the neck mass from 2017. Using the Ig Kappa probe, the same peaks were identified in Tubes A and B. There was an additional peak in the cervical mass, of uncertain significance. The presence of rearrangement of the kappa deleting element is consistent with the expression of lambda in this tumor. The cervical mass also showed a rearrangement of IGH Framework II, but due to poor DNA quality in the older 2012 specimen, no amplification was seen with FR II. MYD 88 mutations were investigated by digital PCR and were negative.
Proposed diagnosis: Crystal storing histiocytosis obscuring extranodal marginal zone lymphoma.
Interesting feature(s) of submitted case: Crystal storing histiocytosis is a rare disorder characterized by aggregates of histiocytes with abnormal intracytoplasmic crystals. In most cases the histiocytosis occurs in association with a B-cell lymphoproliferative disorder, usually lymphoplasmacytic lymphoma, multiple myeloma, or monoclonal gammopathy of uncertain significance (MGUS); however, it has also been described in inflammatory and autoimmune conditions including rheumatoid arthritis. In the current case, the histiocytic proliferation obscured the underlying marginal zone lymphoma, leading to a delay in diagnosis. The histiocytic component was a prominent feature of all the lesions in this patient, both in the ovary in 2012 and the subsequent soft tissue and breast biopsies in 2017. The mechanism by which the crystals accumulate within the histiocytes is not known, but it is thought to be due to the structural properties of the immunoglobulin in combination with high levels of the immunoglobulin in the serum.

EAHP18-LYWS-202

B-cell lymphoid proliferation in a patient with marginal zone lymphoma- reactive or malignant?

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Case description: The patient is a 69 year old female who presented with weight loss, abdominal pain, and vomitting. Gastroscopy with biopsy showed an extronodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), H. pylori positive. Blood counts and LDH levels were normal. The patient received antibiotic treatment for the H. pylori with good clinical response; no residual gastric disease was detected.
Staging studies with PET-CT showed thickening of the small bowel wall with increased FDG uptake. Enlarged mesenteric nodes were seen (up to 2.5 cm. in greatest dimenstion).
In light of these findings, a diagnostic laparatomy with small bowel resection was performed. The small bowel wall was thickened and hard. The mucosal surface showed ulceration with a cobblestone pattern.
Biopsy fixation details: The small bowel was fixed in formalin.
Frozen tissue available: No frozen matieral is available.
Details of microscopic findings: The mucosal surface of the small bowel shows ulceration, consistent with ischemic changes.
Multiple nodules of small lymphoid cells are present in the lamina propria and on the serosal surface. These are comprised primarily of small slightly irregular cells. Occasional plasma cells are interspersed. A significant population of large cells is not seen.
The mesenteric nodes appear reactive.
Immunophenotype: The cells of the lymphoid aggregates are positive for CD20 and CD79a, and are negative for CD3, CD5, CD10, CD23, CD43, and cyclin-D1.
Cytogenetics: Cytogenetic studies were not performed.
Molecular studies: Clonality of the B cells was interrogated by examination of the FR2 and FR3 regions of the IgH gene by PCR. These studies failed to show clonality.
Proposed diagnosis: Benign lymphoid proliferation of B cells in the bowel wall of a patient with marginal zone lymphoma.
Interesting feature(s) of submitted case: We believe that this is an intersting case from the pathologic perspective since it involves the difficult differential diagnosis between a benign and malignant proliferation of B cells in a patient known to have extranodal marginal zone lymphoma. The location, number of lymphoid nodules, and immuoperoxidase results are suggestive of involvement by lymphoma, yet this impression is not supported by the gene rearrangement studies.

EAHP18-LYWS-208

Dural B-lymphoblastic lymphoma with challenging morphology mimicking diffuse large B-cell lymphoma.

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Case description: In 2014, D8-D9-D10 medullary compression. Diagnostic of DLBCL in a peripheral hospital and treatement by polychemotherapy with complete remission, consolidated by a bone marrow autograft. Relapses in 2015 and 2016 of bone lesions treated by polychemotherapy and bone marrow allograft conditionned by a total body irradiation.
In 2017, headache with photo-phonophobia and fever. The patient is transfered to our institution. Cerebrospinal fluid analysis shows blasts. Original tissue block and slides from the 2014 biopsy are sent for second opinion. Our diagnosis : B-lymphoblastic lymphoma.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Massive infiltration of fibro-adipose tissue by a monomorphous proliferation of medium-sized cells with rounded nuclei. The chromatin is clear and there is prominent nucleoli. There's numerous mitosis and some apoptotic figures.
Immunophenotype: - IHC (2014 biopsy) : CD20-, CD79a+, PAX5+, CD10+, TdT+, CD3-, Ki67 70%, EBER-
- Flow cytometry (2017 CSF) : CD45 very low, CD34+, CD19/CD20/CD22+, no surface light chain expression
Cytogenetics: - FISH (2014 biopsy and 2017 CSF) : BCR and ABL1 genes fusion
Molecular studies: - RT-qPCR (2017 CSF) : detection of a BCR-ABL transcript
- PCR (2017 CSF) : B-cell monoclonality
Proposed diagnosis: BCR-ABL1 positive B-lymphoblastic lymphoma
Interesting feature(s) of submitted case: - Morphology mimicking DLBCL
- BCR-ABL1

EAHP18-LYWS-209

Hepatosplenic gamma-delta T-cell lymphoma in a 26-year-old man with ulcerative colitis.

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Case description: The patient was a 26-year-old man with 9-year history of ulcerative colitis and primary sclerosing cholangitis (PSC) controlled with 6-MP, azathioprine and vedolizumab. He developed jaundice in 05/2017 and was found to have significant hepatosplenomegaly. A liver biopsy (06/2017) was consistent with primary sclerosing cholangitis, with involvement by hepatosplenic gamma-delta T-cell lymphoma. A bone marrow biopsy (06/2017) was also involved by lymphoma. After 4 cycles of etoposide, ifosfamide/Mesna, cytarabine and methotrexate (IVAC) complete remission on marrow biopsy and by imaging was obtained (09/2017). In November, he underwent orthotopic liver transplantation for hepatic failure. Both native liver (3280 g) and spleen (1920 g) showed extensive involvement by lymphoma. In December 2017, he was admitted for fevers and increasing liver function tests. A biopsy showed recurrent lymphoma in the hepatic allograft. The patient is currently being treated with pentostatin.
Biopsy fixation details: All samples were formalin-fixed and paraffin-embedded except for the bone marrow biopsies that were fixed in B+ fixative and decalcified with Rapid Cal solution.
Frozen tissue available: No.
Details of microscopic findings: The initial liver biopsy showed lymphocytic cholangitis, with bile duct injury and bridging fibrosis and occasional nodule formation consistent with PSC (stage 3-4/4). Sinusoids were expanded by small to medium-sized atypical lymphoid cells with oval to markedly irregular and clefted nuclei. The bone marrow biopsy revealed a predominantly intrasinusoidal lymphocytic infiltrate accounting for about 20% of the overall marrow cellularity.
The explanted native liver showed similar morphologic features with extensive sinusoidal involvement by lymphoma. The spleen also showed extensive infiltration of the red pulp by lymphoma.
The most recent hepatic allograft biopsy showed involvement by lymphoma with morphologic and immunophenotypic features similar to those in the prior samples.
Immunophenotype: By immunohistochemistry, the lymphoid cells were positive for CD3 and CD2, CD8, CD56, CD7 (partial), perforin (partial, mostly negative), and were negative for CD5, CD4, CD20, PAX5, BetaF1, and Granzyme B. Epstein-Barr virus encoded RNA (EBER) was negative. Flow cytometry on the bone marrow showed 11% abnormal T cells with the following immunophenotype: CD3dim, CD2+, CD7+, CD4-, CD8+/-, CD57-, CD56+, CD16-, TCRα/β-, TCRγ/δ+, TdT-, CD1a-.
Cytogenetics: Karyotype performed on bone marrow aspirate: 45,X,-Y,i(7)(q10),add(16)(q24)[3]/46,XY[17].
Molecular studies: No mutations were identified with SNApShot assay (Next Generation Sequencing, Myeloid panel, 54 genes; biliary brush).
Proposed diagnosis: Hepatosplenic T-cell lymphoma (γ/δ phenotype).
Interesting feature(s) of submitted case: The clinical and pathologic findings were typical for hepatosplenic T-cell lymphoma. However, the case presented some challenging aspects. The diagnosis in the initial liver biopsy was made more difficult by the background PSC and the subtle intrasinusoidal neoplastic infiltrate. A reactive process was initially entertained until immunostains were done. Of note, karyotype showed i(7), a finding characteristic of this entity. This patient received a liver transplant for his underlying PSC and the lymphoma relapsed in the allograft only 1 month after transplantation despite prior apparent remission in the bone marrow. There is little very data on the propensity of hepatosplenic T-cell lymphoma to relapse in transplanted liver but, in this case, chronic immunosuppression possibly favored not only the onset but also the recurrence of the lymphoma.

EAHP18-LYWS-216

Clonal CD4+ T-lymphoproliferative disease with indolent features confined to the testicle

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Case description: White man (born in 1945), with a two-year history of itchy rash and no lymphoma risk factors, was found to have high PSA (65 ng/mL) which led to the diagnosis of a prostate cancer (Gleason 3+4, T2a). Subsequent ultrasound and CT showed an enlarged right testicle. No other significant changes were detected on pelvic MRI and a bone scan. The enlarged firm testicle was painless. No B-symptoms were present. A skin biopsy was interpreted as eczema in another institution (to be reviewed). The right testicle has been resected, revealing a lymphoproliferative process submitted to this Workshop.
Staging bone marrow trephine (reported in the referring institution) and bone marrow flow cytometry (done at the University of Birmingham Hospital) did not reveal any abnormal lymphoid populations. Flow cytometry of peripheral blood showed 2.3% B-cells with no light chain restriction and 6.9% T-cells with an abnormal CD4:CD8 ratio of 15:1 ; however, with no T-cell clonality by BIOMED2 (at UHB). A low-level IgM paraprotein (~5g/L) was noted. Full blood counts, liver function tests and LDH were normal.
The prostate cancer was treated with hormonal therapy and radiotherapy, and the patient remains in remission. No treatment was applied for the testicular lymphoproliferative lesion and the patient remains well, without any signs of progression since the diagnosis in Nov 2015.
Biopsy fixation details: Orchidectomy, routinely processed (formalin/paraffin)
Frozen tissue available: No
Details of microscopic findings: Most of the testicle is involved by a dense lymphoid infiltrate dominated by small mitotically inactive T-lymphocytes with slightly irregular nuclei which invade the seminiferous tubules. There are also scant clusters of small bland B-cells; plasma cells are not conspicuous. The epididymis is largely spared. No necrosis, striking atypia or large cell infiltrate can be seen.
Immunophenotype: [1] Dominant T-cells: CD3+, CD2+, CD5+, CD7-/+ (down-regulated), CD4+, CD8-, PD1+/- (many positive, not strongly), CD10-, BCL6-, CD57+/- (similar to PD1), CD56-, Granzyme B-, CD20-, CD79a-, PAX5-, CD30-, ALK1-, CD25-, Cyclin D1-, BCL2-/+. Virtually non-proliferative in ki67.
[2] Scant B-cells: CD20+, PAX5+, CD79a+, CD10-, BCL6-, CD138-, ki67 negative. No light chain restriction. EBV EBER-
Cytogenetics: Not done
Molecular studies: (BIOMED2 PCR on deparaffinised orchidectomy sections):
TCR-Beta-A, TCR-Beta-B: polyclonal
TCR-Beta-C, TCR-Gamma-A, TCR-Gamma-B: monoclonal
IGH FR3: dominant/monoclonal peak + polyclonal background
IGH FR2 & IGH FR2: irregular/ non-reproducible, poor amplification
Proposed diagnosis: Clonal CD4+ T-lymphoproliferative disease with indolent features confined to the testicle.

Interesting feature(s) of submitted case: This tumour does not fit well into the existing WHO classification of lymphoproliferative lesions. There are some analogies to the indolent T-cell lymphoproliferative disorder of the GI tract and to the primary cutaneous CD4 positive small/medium T-cell LPD. Various epithelial organs may be affected by a group of indolent clonal T-cell proliferations [Hum Pathol 2013;44:1927] and thiscase likely represents a testicular example of this spectrum of still poorly defined diseases.
Limited evidence of concomitant B-cell clonality by PCR may be related to the MGUS-type paraproteinaemia and most likely is unrelated to the T-lymphoproliferative process, although T-cell lymphomas associated with clonal B-cell proliferations unrelated to EBV are well documented in the literature [Am J Surg Pathol 2007;31:1310].

EAHP18-LYWS-223

Solitary B-Lymphoblastic Lymphoma of the Jejunum

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Case description: A 12 year old girl presented herself in April 2014 having intermittent stomach pain over the past 8 months and vomiting daily since January of that year. Her weight dropped from 45Kg to 39Kg in the last month and she was unable to attend school for the last 3 weeks. She was only able to take liquid foods in the week before admittance. Clinical assessment revealed some discomfort just below her belly button. Upon palpitation, this area also felt somewhat firm. An abdominal ultrasound and a MRI showed an obstruction in the jejunum with a somewhat polypus appearance and dilatation of the jejunum proximal to this lesion. The lesion was surgically resected and submitted to our department for pathological examination. Upon diagnosis a staging bone marrow aspirate and liquor analysis was performed and both showed no involvement.
Biopsy fixation details: 10% neutrally buffered formalin and routinely processed.
Frozen tissue available: No
Details of microscopic findings: An obstructing, moderately sharp defined lesion in the wall of the intestine, without perilesional fibrosis was found. The lesion extended through the submucosa and muscular layer of the jejunum into the surrounding fatty tissue. The lesion consists of small to medium sized atypical blastoid cells which are arranged in sheets. The blasts have an irregular nucleus with a fine chromatin pattern and sometimes a discrete nucleolus. The cells have moderate amount of cytoplasm and mitotic figures are easily seen.
Immunophenotype: The immunohistochemical analysis on sections of the FFPE tissue revealed strong positivity of the blastoid cells for CD79a, CD10, BCL2 and TdT with a very high proliferation of approx. 80% (MIB1 staining). CD45 was weakly positive in a minority of the blastoid cells. The stainings for CD34, CD117, MPO, Lys, CD20, MUM1, BCL6, cyclinD1, CD4, CD8, CD2, CD7 and CD56 were negative. There are scattered FDC networks present as seen in the CD21 and CD23 stainings. CD3 and CD5 demonstrate scattered small T-cells in the lesion.
Cytogenetics: N/A
Molecular studies: N/A
Proposed diagnosis: Solitary B-lymphoblastic lymphoma of the jejunum
Interesting feature(s) of submitted case: To our knowledge, the sole location of a B-lymphoblastic lymphoma in the jejunum without involvement of other locations has not yet been described in the literature. In addition, this is a macroscopically well documented case.

EAHP18-LYWS-234

Philadelphia chromosome positive cutaneous Diffuse Large B-Cell Lymphoma (DLBCL) developed in a patient with Chronic Myeloid Leukemia (CML), Chronic phase, Is it a Richter-Like transformation?

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Case description: Our patient is 41 year old male presented with dizziness and blurred vision and found to have anemia, thrombocytopenia and hepatosplenomegaly. The bone marrow was hypercellular for age (80%), composed mainly of myeloid precursors with left shifted maturation. The diagnosis of (CML) has been established, and confirmed cytogenetically by detection of t(9;22)(q34;q11). Five months later, the patient was admitted due to hematemesis and severe weight loss. On examination found to have pancytopenia and a cutaneous nodule on the upper chest. A biopsy was taken from the nodule and diagnosed as ph+ Diffuse Large B-Cell Lymphoma (DLBCL). The staging bone marrow was positive for involvement by DLBCL and the patient started receiving R-CHOP chemotherapy. The development of ph+ DLBCL in a ph+ CML patient raises the question of clonally related transformation of CML in a way similar to what is seen in transformation of Chronic Lymphocytic Leukaemia (CLL) patients (Richter transformation).
Biopsy fixation details: Peripheral blood smears and bone marrow aspirates were air dried and stained with Leishman stain. The skin nodule and bone marrow trephine biopsies were fixed in 20% non-buffered formalin. Paraffin-embedded specimens were stained with routine Hematoxylin and Eosin (H&E) for histologic diagnosis. The eight color flowcytometric analysis was performed on a BD FACSCanto instrument (BD Biosciences, san Jose, Ca, USA).
Frozen tissue available: Not available
Details of microscopic findings: Peripheral blood smear: revealed numerous myeloid precursors and normocytic normochromic anemia.
Bone marrow: hypercellular for age (80%), mainly composed of myeloid precursors with left shifted maturation and monolobated megakaryocytes. the blasts were not increased (<1%). The diagnosis of chronic myeloid leukemia (CML) was established.
Skin biopsy: sheets of large atypical lymphocytes, dissecting deep and effacing normal architecture.
Immunophenotype: The tumor cells within the DLBCL were immunoreactive for CD79a, D10, Bcl-2, CD43, and focally for MUM-1; and immunonegative for CD5, Bcl-6, EBV, MPO, CD117, and CD68. the proliferative index (Ki-67) was estimated at 50%.
Cytogenetics: Diagnostic PB/BM: t(9;22)(q34;q11)
Involved marrow by DLBCL: Karyotyping of 27 metaphases from the bone marrow infiltrate revealed that 8 metaphases of them were normal “46,XY”, 12 metaphases exhibited “46, XY, t(9;22)(q34;q11)”; and 7 metaphases showed “47, XY, +8, del(6q), t(1;9)(q11;p11), and t(9;22)(q34;q11)"
Follow up marrow post RICE chemotherapy: Karyotyping of 60 metaphases from the bone marrow infiltrate revealed that 55 metaphases were normal “46,XY”, and 5 metaphases showed “46, XY, t(9;22)(q34;q11)”only.
Molecular studies: FISH analysis on skin nodule is positive for BCR/ABL and negative for BCL2, BCL6, and MYC genes rearrangement.
Proposed diagnosis: Philadelphia chromosome positive cutaneous DLBCL developed in a patient with Chronic Myeloid Leukemia, Chronic phase, Is it a Richter-Like transformation?
Interesting feature(s) of submitted case: To our knowledge, this is the only case to report a transformation of CML, chronic phase patient into a Philadelphia chromosome positive cutaneous DLBCL in a manner similar to what been described in CLL, Richter transformation.

EAHP18-LYWS-243

Primary extranodal marginal zone lymphoma (MALT-lymphoma) of the liver in a patient with Sjögren's syndrome

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Case description:
66-year-old female with an unclear lesion of the liver in segment IV, suspected as cholangiocellular carcinoma in diagnostic MRI-scan. Two years earlier, the patient was diagnosed as Sjögren's syndrome with xerophthalmia, elevated ANA (1:10.000) and SSA (4.88) antibodies, hypergammaglobulinemia (20%) and no visceral manifestations. Resection of the lesion showed pathohistologically an extranodal marginal zone lymphoma (MALT-lymphoma) of the liver. BM biopsy without lymphoma infiltrates, no evidence for dissemination in further staging.
Biopsy fixation details: formalin-fixed liver tissue
Frozen tissue available: frozen tissue available
Details of microscopic findings: The liver shows extensive nodular lymphoid infiltrates between regular liver tissue with less than 5 % steatosis. The lymphoma shows a perifollicular concentric growth pattern with nonneoplastic germinal centers with focal colonization and partially preserved mantle zone, the neoplastic cells are primarily arranged in the perifollicular region and predominantly show monocytoid appearance. Lympho-epithelial lesions can be found, one examined hilar lymph node shows very focal neoplastic infiltrates.
Immunophenotype: The neoplastic population shows positive reaction for CD20, negative reaction for CD10, bcl6, MUM1, CD5, cyclin D1, CD23, CD43, cIG, IgD.
Cytogenetics: Not done.
Molecular studies: FISH showed no evidence of breaks of IGH and MALT1. Further molecular studies (panel sequencing) pending, will be presented.
Proposed diagnosis: primary extranodal marginal zone lymphoma (MALT-lymphoma) of the liver
Interesting feature(s) of submitted case: This case shows a rare example of MALT-lymphoma of the liver. Primary hepatic lymphomas account for 0,016% of all cases of Non-Hodgkin-lymphomas. Among these, MALT-lymphomas are extremely rare. The etiology of MALT-lymphomas of the liver remains unclear, but is often related to chronic-inflammatory disorders (Hepatitis B and C, PBC and HP-infection) and autoimmune disease (Sjögren's syndrome) like in this case.

EAHP18-LYWS-245

Laryngeal mucous membrane plasmacytosis with 15-year follow-up.

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Case description: The patient is a 68-year old female with a history of COPD and smoking, who presented with a long history of dysphagia due to a persistent laryngeal lesion. A biopsy of this lesion in 2002 showed a prominent submucosal plasmacytosis. Definitive evidence of clonality was not seen by immunohistochemical or molecular testing. The patient had normal serum immunoglobulin levels and serum protein immunofixation was negative for monoclonal proteins. Complete blood count and chemistry tests were within normal limits. No additional masses were identified. The patient had localized cervical lymphadenopathy in 2002 that was biopsied and revealed a reactive lymph node with nonspecific paracortical hyperplasia and interfollicular plasmacytosis with polytypic plasma cells. Flow cytometry of the lymph node was unremarkable and molecular studies were negative for clonal gene rearrangements.
The patient was treated with low dose prednisone which relieved the dysphagia. The patient experienced a waxing and waning course over the next 15 years that was responsive to steroid therapy. She recently re-presented in 2017 with mild enlargement of a papillomatous laryngeal lesion and a repeat biopsy of the lesion was performed.
Biopsy fixation details: Zinc buffered formalin. **Frozen tissue available:** No
Details of microscopic findings: The sections from the laryngeal biopsy showed squamous mucosa with nodular psoriasiform epithelial hyperplasia. No epithelial dysplasia was seen. There was neutrophilic inflammation of the epithelium with occasional microabscesses. A prominent, dense, submucosal infiltrate composed primarily of plasma cells was present. Plasma cells appeared mature with round nuclei and without prominent nucleoli. The findings of the 2002 and 2017 biopsies were similar.
Immunophenotype: Immunohistochemical studies showed that the plasma cells were positive for CD138 (variable expression) and CD38; and negative for CD56, CD20, cyclin D1 and HHV8. Kappa and lambda IHC and ISH studies showed a mildly elevated kappa:lambda ratio, but definitive evidence of monotypic light chain expression was not seen. EBER ISH was negative. GMS and spirochete stains were negative for microorganisms.
Cytogenetics: Not performed
Molecular studies: Molecular PCR studies performed in 2002 were negative for clonal IGH gene rearrangements. In the biopsy from 2017, PCR studies showed an equivocal gene rearrangement of the IGH gene in a polyclonal background, and no clonal rearrangements of IGK, IGL, and IGK deleting element.
Proposed diagnosis: Mucous membrane plasmacytosis
Interesting feature(s) of submitted case: Mucous membrane plasmacytosis is a rare, benign condition with only about 30 cases reported in the English literature. There has been limited molecular data reported and most cases provided relatively short clinical follow-up (<5 years). Most of the reported cases involved the upper aerodigestive tract and presented with papillomatous or cobblestone lesions causing dysphagia or dysphonia. In this patient, a mucosal mass-like proliferation of plasma cells was well documented over a period of 15 years. No definitive evidence of clonality could be demonstrated by immunohistochemical or molecular methods. The patient also did not exhibit clinical or laboratory manifestations of a systemic plasma cell disorder. The laryngeal lesion showed good response to low dose prednisone, which resulted in improvement of the patient's dysphagia, but exhibited a waxing and waning course. Overall, the process demonstrates striking persistence in anatomic site and histology with a relatively indolent clinical course.

EAHP18-LYWS-254

Pulmonary atypical lymphoid infiltrate highly suspicious for indolent T cell lymphoproliferative disorder.

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Case description: 69 year-old male, retired mechanic and ex-smoker with 40 pack year history stopped in 2002. History of several bronchial mucosa biopsies (2000 & 2003) showing mild dysplasia. Previous myocardial infarction (2010) and abdominal aorta aneurysm (2016). Recent findings of incidental left lower lung lobe nodules (1.2 & 2.0 cm) and right pleural thickening. They were moderately FDG-avid by PET (max 4.6). There is no evidence of lymphadenopathy, hepatosplenomegaly or skin lesions.
Biopsy fixation details: Left lower lobe resection fixed in 10% Neutral Buffered Formalin.
Frozen tissue available: Not performed.
Details of microscopic findings: There is a large nodular mass extending from the pleura into the lung parenchyma. It shows poorly circumscribed margins with infiltration around the nodule extending around bronchi and vessels. The infiltrate is diffuse and composed of small, medium, and rare large lymphoid cells, abundant histiocytes, plasma cells, and scanty neutrophils and eosinophils. Rare and scattered large lymphoid cells with polylobated nuclei and prominent nucleoli are noted. Classical Hodgkin or Reed-Sternberg cells are not identified. Mitotic figures are present but rare. There are no necrotic areas, granulomatous aggregates or angiocentric lesions. Microorganisms are not seen on special stains (ZN, PAS-D, GMS). The lung tissue away from the nodules shows background emphysematous changes.
Immunophenotype: The small to medium lymphoid cells are CD3+ T cells with rare focal aggregates of small CD20+ B cells. Scattered interspersed large B cells are noted with variable CD20/PAX5 expression. These cells do not form clusters or sheets. Some large cells are variably positive for CD30 and negative for CD15. They are MUM1+, focally positive for BCL6 and negative for CD10. The CD21 and CD23 highlight some small follicular dendritic networks associated with clusters of small B cells. The T cells are small/medium sized with both frequent CD4+ and abundant CD8+ T cells. Many T cells are positive for both CD57 and PD1 and show partial dim/loss of BCL2. The CD8+ cells are positive for both TIA1 and Granzyme B. The T cells are positive for TCR betaF1 with only very rare cells TCR gamma/delta+ seen. The plasma cells are polytypic. EBV EBER ISH is negative. Ki-67 shows a low proliferative rate of approximately 15%. The stain for keratin highlights partially preserved underlying pulmonary architecture with no lymphoepithelial lesions.
Cytogenetics: Not performed.
Molecular studies: BIOMED 2PCR analysis was performed twice and showed a T cell clone present in one TCRB reaction that persisted in both PCR tests. A borderline B cell clone was present in only one of the repeated IgH PCR tests.
Proposed diagnosis: Atypical lymphoid infiltrate highly suspicious for indolent T cell lymphoproliferative disorder.
Interesting feature(s) of submitted case: The overall morphology when taken in conjunction with the T-cell clonality is highly suspicious for a clonal T-cell lymphoproliferative disorder (LPD). However, the indolent morphology of this lesion likely localized to the lung and clinically asymptomatic hampers the definitive diagnosis of malignancy as PTCL, NOS. Primary lung PTCL, NOS are very rare and described as morphologically and clinically very aggressive. The indolent morphology of the current lesion composed of abundant CD8+ T cells but also frequent CD4+ and PD1+ T cells admixed with frequent histiocytes and plasma cells favors an indolent clonal T cell LPD. Some features suggest the recently redefined primary cutaneous CD4+ small/medium T-cell LPD. Could this represent a primary pulmonary counterpart?

EAHP18-LYWS-268

Atypical lymphoid hyperplasia of the bowel due to activated phosphoinositide 3-kinase delta syndrome (APDS).

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Case description: Boy of 6 years with known hypogammaglobulinaemia and chronic relapsing autoimmune haemolytic anaemia (AIHA) presented with colicky abdominal pain due to intestinal obstruction. He had had a community acquired pneumonia age 4. He was treated with subcutaneous immunoglobulin and the AIHA was treated with rituximab, prednisolone and mycophenolate. He had no past other medical history of note and was immunised according to the UK childhood vaccination schedule.
At laparotomy he was found to have mesenteric lymphadenopathy and a hard tumour 115cm proximal to the ileocaecal valve.
Macroscopic
80mm of small bowel was received and there was a firm mass 40mm in diameter encircling the bowel. The lumen was narrowed and the bowel proximal to the obstruction was dilated. The mass showed a homogeneous white cut surface. There were enlarged lymph nodes in the attached mesentery.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: The sections from the area of bowel wall thickening show a dense infiltrate of lymphoid cells throughout the bowel wall. These are associated with some enlarged adjacent lymph nodes. The lymph nodes appear to show some maintenance of the normal architecture with patent sinuses and small lymphoid follicles. The lymphoid infiltrate within the bowel wall has a vaguely nodular architecture. The overlying mucosa is partially ulcerated and replaced by granulation tissue. The infiltrate is composed predominantly of small and medium sized lymphoid cells with admixed histiocytes, plasma cells and occasional scattered larger blast cells.
Immunophenotype: The vast majority of the cells present within the infiltrate are T-cells and show expression of T-cell markers CD2, CD3, CD5 and CD7. CD20 and CD79a shows scattered cells throughout the main infiltrate and some of these are larger blast cells. The T-cells are predominately CD8 positive with fewer CD4 positive cells. Ki67 demonstrates a relatively low proliferation fraction and there is no evidence of TDT expression. Immunoglobulin light chain staining demonstrates a polytypic population of plasma cells and small numbers of B-cells within the infiltrate.
Cytogenetics: Not performed
Molecular studies: Polyclonal TCR & IgH gene rearrangements were detected consistent with polyclonal lymphocyte populations.Molecular data consistent with polyclonal TCR/Ig gene rearrangements with no evidence of T- cell clonality.
Sequencing
Whole exome sequencing was perfomed and analysed against a virtual panel of immunodeficiency genes and this identified a variant PIK3CD associated with activated phosphoinositide 3-kinase d syndrome (APDS).
Proposed diagnosis: Atypical lymphoid hyperplasia due to APDS
Interesting feature(s) of submitted case: Patients with APDS suffer frequent sinopulmonary infections due to impaired humoral immunity, autoimmune phenomena and lymphoid hyperplasia due to immune dysregulation.

EAHP18-LYWS-269

LPD in gastrointestinal tract, excluding gastric marginal zone lymphoma

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Case description: Male 63 years; HIV negative; development of a progressively worsening abdominal pain for which a CT scan was performed revealing a 10 cm ileal mass; PET scan showed multiple skeletal lytic lesions. The mass was surgically removed. Staging procedures documented marrow involvement by the more aggressive cell subset.
The patient is about to start chemotherapy with HYPERCVAD-scheme.
Biopsy fixation details: 36 hour 10% buffered formalin and paraffin embedding
Frozen tissue available: No frozen tissue available
Details of microscopic findings: Massive ulcerative transmural infiltrate, with diffuse growth and made by two topographically separated cell components with little areas of admixture.
The first cell subset is represented by small bland looking lymphocytes with mildly pale cytoplasm and vaguely nodular growth; the second cell subset is made by sheets of large cells with prominent nucleoli with plasmablastic features. Within these areas scattered CD20+ nodules made of the small cells are observable
Immunophenotype: Small cell subset: CD20+, CD79+, CD3-, IRTA1+, MNDA-+, CD138-, Cyclin D1-, IRF4-, CMYC-, K/L not contributory, BCL2+,CD10-,KI67 low
Large cell subset: CD20-, CD138+, IRTA1-, MNDA-, CD79-, Lambda+, CMYC+ (50%), IRF4+, BCL2-,CD10+ Ki67 high
EBV negative
Cytogenetics: Not performed
Molecular studies: PCR (Euroclonality protocols) performed separately in the two different dissected areas
Small cell areas: IGH 132bp clone in oligoclonal background; IGK oligoclonal pattern
Large cell areas: IGH 132bp clone in oligoclonal background; IGK oligoclonal pattern
IgH analysis: the oligoclonal background is different in the two samples;
IGK analysis: the pattern is overlapping in the two areas.
FISH:
Small cell areas: t(11;18)(q21;q21) negative; 8q24 BA negative
Large cell areas: t(11;18)(q21q21) negative; 8q24 BA positive
ISH:
EBER1/2 probe negative in both areas
Proposed diagnosis: Large B-cell Lymphoma with plasmablastic features transformed from a marginal zone B-cell lymphoma, extranodal/MALT type
Interesting feature(s) of submitted case: Plasmacellular differentiation in MALT lymphomas is well acknowledged, while its differentiation into highly proliferating plasmablasts is exceedingly rare; the case shows clonal relationship between the two cell subsets and the acquisition of a 8q24 translocation in the high grade subset as possible driver for the aggressive transformation. No previous therapy with standard or biologic drugs were reported which could play possible roles in the plasmablastic transformation

EAHP18-LYWS-331

Burkitt lymphoma presenting as a posterior mandibular mass a patient with chronic lymphocytic leukemia

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Case description: A 48-year-old man with history of hepatitis C infection and polysubstance abuse presented with leukocytosis in 2011 and was diagnosed with chronic lymphocytic leukemia (CLL). He was lost to follow up until presenting to the emergency department in October 2017 with increasing lower back pain and progressive bilateral lower extremity weakness. He was found to have a WBC of 223,000/uL with 97% lymphocytes and flow cytometry on peripheral blood (PB) was consistent with CLL. Imaging studies demonstrated extensive spinal and leptomenigeal involvement. Evaluation of cerebrospinal fluid was negative for involvement by lymphoma. He was treated with three doses of rituximab, intrathecal cytarabine and methotrexate, and a course of radiation therapy to his spine.
In December 2017, he was readmitted for intractable pain and found to have lymphomatous involvement of the left kidney, as well as multiple subcutaneous and retroperitoneal lesions. He received fludarabine, cyclophosphamide, and rituximab. He was also found to have extensive dental disease requiring multiple tooth extractions. A biopsy from a posterior mandibular lesion was diagnostic for Burkitt lymphoma (BL). At the end of the month, he was admitted for cycle 1 of R-EPOCH.
Biopsy fixation details: Received in formalin are multiple fragments of tan-yellow, soft, rubbery tissue obtained from oral cavity and measure 2.5 x 2.5 x 1.0 cm in aggregate.
Frozen tissue available: None
Details of microscopic findings: Evaluation of peripheral blood demonstrates significant lymphocytosis with 97% lymphocytes that are small to intermediate in size with round nuclear contours, parachromatin clumping, and scant pale blue cytoplasm. Red blood cells and platelets are unremarkable.
Microscopic evaluation of oral tissue shows a diffuse infiltrate of intermediate-sized lymphocytes with round to polygonal nuclear contours, mature chromatin, occasional small nucleoli, and scant amphophilic cytoplasm. Mitotic figures and tingible body macrophages are readily identified.
Immunophenotype: Flow cytometry (PB): Positive for CD19, CD20 (dim), CD5, CD23, CD45, bright CD200, and dim lambda light chain. Negative for CD10 and CD49d (93% of total events).
Immunohistochemistry (oral lesion): Positive for CD20 (dim), CD10, BCL6, LEF1, MYC, and Ki67 shows a proliferation index approaching 100%. Negative for TdT, BCL2, CD34, and CD5.
Cytogenetics: FISH (PB): Positive for deletion of the 13q 14.3 region.
FISH (oral lesion): Positive for MYC rearrangement using break-apart probes and negative for BCL2 and BCL6 rearrangements.
Molecular studies: Immunoglobulin variable region somatic mutation analysis (IGHV) (PB): Hypermutated status.
EBV in situ hybridization (EBER) (oral lesion): Negative.
Proposed diagnosis: Burkitt lymphoma and chronic lymphocytic leukemia
Interesting feature(s) of submitted case: 1. It is unknown if the BL represents a transformation from CLL or is de novo BL.
2. LEF1 is expressed in CLL but is also commonly expressed in cases of sporadic BL (Am J Pathol 2013;182(4):1092-8).
3. High grade transformation from IGHV-hypermutated CLL (such as this case) has a higher rate of being clonally unrelated to CLL. Therefore, comparative IGHV mutation testing on both the CLL and BL may not have significant diagnostic utility.

EAHP18-LYWS-338

Plasmablastic variant of Richter transformation

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Case description: The patient was a 65 year-old HIV-negative Caucasian male with a history of chronic lymphocytic leukemia (CLL) diagnosed in 2008, who was treated with FCR, R-CVP, and later ibrutinib. In 2016, a bone marrow biopsy showed persistent involvement by CLL with a complex karyotype, FISH evidence of deletion of TP53, and mutations in TP53 and SF3B1. In April 2017 he was treated with obinutuzumab but bone marrow biopsies collected in May and July 2017 showed persistent extensive involvement by CLL with the same cytogenetic abnormalities seen in 2016. In October 2017, the patient presented with a 5.7 cm mass filling the right maxillary sinus and protruding into the right nasal cavity. Biopsies of the nasal mass were obtained. A serum IgG lambda serum paraprotein was identified (estimated at 0.5 g/dL). The patient was treated with R-EPOCH (to which he responded partially) and died two months after the biopsy of the nasal mass was performed.
Biopsy fixation details: Neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: H&E-stained sections show fragments of benign respiratory-type mucosa with a dense atypical infiltrate of large plasmacytoid cells with round to oval and occasionally irregular nuclei, vesicular or fine chromatin, prominent central nucleoli, and abundant amphophilic cytoplasm with rare to occasional perinuclear hofs. The cells of this infiltrate are seen forming sheets with frequent tingible-body macrophages, apoptotic bodies, and mitoses. A "starry sky" appearance is seen at low magnification,
Immunophenotype: The large atypical plasmacytoid cells are positive for CD138, MUM1, lambda, CD10, CD56(minor subset), MYC(>90%), and Ki67 (~80%) and negative for CD45, CD20, PAX5, CD3, CD5, BCL2, BCL6, CD23, CD30, CD117, kappa and EBER(ISH).
Cytogenetics: FISH studies were positive for MYC (8q24) rearrangement (48/100 cells, unknown partner), gain of CKS1B (1q21) (84/100 cells), TP53 (17p13.1) deletion (heterozygous in 62/100 and homozygous in 30/100 cells), and monosomy 12 (95/100 cells).
FISH studies showed low positive results for loss of CDKN2C (1p32) (31/100 cells), monosomy 13 (33/100 cells), and gain of IGH (14q32) (38/100 cells).
FISH studies were negative for t(4;14), t(11;14), t(14;16), trisomy 12, and ATM deletion.
Molecular studies: Gene sequencing studies revealed the following mutations: a disease-associated variant in TP53 (p.E198*, c.592G>T, VAF: 82%) and a variant of uncertain significance in NRAS (p.A59G, c.176C>G, VAF: 59%).
Comparative IGH gene rearrangement studies by PCR performed on the large atypical plasmacytoid cells from the nasal mass, and the CLL cells from a bone marrow aspirate collected in May 2017 showed a clonal rearrangement in framework 3 in both specimens with identical 124 base pairs peaks. These findings provide evidence of clonal relationship between the high-grade infiltrate in the nasal mass and the CLL in the bone marrow.
Proposed diagnosis: Plasmablastic variant of Richter transformation.
Interesting feature(s) of submitted case: The differential diagnosis includes transformation of CLL to a plasmablastic lymphoma or a plasmablastic plasmacytoma. However, the lack of expression of CD30, the negative EBER(ISH), and the identification of gain of 1q21 and loss of 1p32 by FISH studies are most compatible with a plasmablastic plasmacytoma than with a plasmablastic lymphoma.
No glass slides from this case will be submitted for review as only one H&E-stained slide from each block is available and the paraffin blocks have been depleted.

EAHP18-LYWS-342

Central nervous system involvement of relapsed classic Hodgkin lymphoma

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Case description:
A 49-year-old man with HIV/AIDS, hepatitis B infection, and history of classic Hodgkin lymphoma presented to the emergency room with a headache.

Six months earlier, he was admitted with fever, hypotension, and profound anemia, and was found to have diffuse lymphadenopathy on subsequent imaging. Excisional biopsy of an inguinal lymph node revealed nodular sclerosis classic Hodgkin lymphoma. Bone marrow staging was negative for involvement. He underwent 2 cycles of ABVD therapy followed by 4 cycles of AVD. Follow-up PET-CT scans confirmed complete disease resolution.

Brain CT and MRI studies were performed as part of the work up for his headache, which detected large left posterior parietal and small right orbitofrontal enhancing masses (2.5 cm and 0.8 cm in greatest dimension, respectively). These masses were associated with significant vasogenic edema and leptomeningeal enhancement. There was no evidence of systemic involvement and bone marrow biopsy was likewise negative. The left posterior parietal mass was biopsied.

Biopsy fixation details: 10% neutral buffered formalin

Frozen tissue available: No

Details of microscopic findings:
The brain biopsy showed neural tissue infiltrated by an abnormal, densely cellular proliferation composed of scattered Hodgkin/Reed-Sternberg (HRS) cells, which were embedded within a mixed inflammatory infiltrate of small lymphocytes, plasma cells, and rare eosinophils. The parenchyma adjacent to the tumor exhibited astrogliosis. Large regions of geographic necrosis were present.

Immunophenotype:
The HRS cells were positive for CD30, CD15, MUM1, and PAX5; they were negative for CD20 and CD45. This immunoprofile was similar to the patient's diagnostic lymph node biopsy.

Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Classic Hodgkin lymphoma (cHL) involving central nervous system (CNS)
Interesting feature(s) of submitted case:
We report a case of cHL with isolated CNS involvement at the time of relapse. CNS involvement of cHL is exceedingly rare, with an incidence as rare as 0.02% in patients with systemic cHL (data from the German Hodgkin study group). Due to its rarity, there are no consensus guidelines on therapeutic management. The patient's disease was not responsive to high dose methotrexate; however, he did exhibit near complete resolution of the intracranial lesions following therapy with the DeAngelis protocol.

EAHP18-LYWS-370

Primary testicular B lymphoblastic lymphoma

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Case description: A 3-year-old Asian male first presented with pain and enlargement of his left testicle that fluctuated in size, without any other symptoms. The mass persisted after a course of antibiotics. Physical examination of the scrotum demonstrated a firm, homogenously enlarged and tender left testicle. The patient underwent a trans-inguinal exploration with an incisional biopsy, which revealed B lymphoblastic lymphoma (B-LBL). No other mass lesion(s) or lymphadenopathy were detected on imaging. Concurrent bone marrow and CSF cytology showed no evidence of lymphoblastic leukemia. Two months later, a post-induction chemotherapy biopsy from the left testicle showed no residual disease. Six years after diagnosis, the patient remains in remission.

Biopsy fixation details: Testicular biopsy was fixed in formalin. Bone marrow biopsy was fixed in Bouin's solution. Fresh tissue was submitted for flow cytometry and cytogenetic and molecular analysis.
Frozen tissue available: None
Details of microscopic findings: The testicular biopsy showed a diffuse, interstitial infiltrate of medium-sized lymphoid cells with ovoid to irregular nuclei, fine chromatin, indistinct or small nucleoli and scant cytoplasm. Mitotic figures were readily observed.
Immunophenotype: Flow cytometry of the testicular mass detected a major population of precursor B-cells, which showed the following aberrant immunophenotype: CD34+, TdT+, CD19+, CD79a+, CD10+, cytoplasmic IgM+, CD20-, HLA-DR+, CD38+ and CD43+. No CD13, CD33, CD117 or MPO expression was noted. The immunophenotypic findings were diagnostic of B lymphoblastic lymphoma. Flow cytometry of the concurrent bone marrow and post-induction chemotherapy testicular biopsy showed no B lymphoblasts.
Cytogenetics: FISH analysis of the testicular mass using TEL/AML1, BCR/ABL, MLL, and p16/CEP9 probes showed Trisomy 21 (87%) and heterozygous deletion of p16 (93.6%), while the B-ALL hyperdiploidy probe panel (CEP 4, CEP 10 and CEP 17) showed Trisomy 10 in 73.5 % cells. These findings were suggestive of a hyperdiploid karyotype. G-Band analysis of the concurrent bone marrow showed a normal male karyotype and FISH analysis using the B-ALL hyperdiploidy panel and p16/CEP9 probes showed no evidence of clonal abnormality.
Molecular studies: The testicular mass showed clonal IGH gene rearrangement products by PCR while TCRβ gene rearrangement analysis showed polyclonal products. The post-induction testicular biopsy was negative for clonal IGH gene rearrangement.
Proposed diagnosis: Primary testicular B lymphoblastic lymphoma
Interesting feature(s) of submitted case: Extramedullary presentation of B lymphoblastic leukemia/lymphoma is not infrequent, with a predilection for the central nervous system, lymph nodes, soft tissue, skin, and spleen. However, testicular infiltration is rare and it usually occurs late in disease course or at relapse. Initial presentation as localized testicular disease is exceedingly rare. A review of the literature disclosed only four other reported cases including one occurring in a pediatric patient. The prognosis is dependent on the genotype and clinical prognostic factors. Appropriate therapy for children presenting with localized disease is still uncertain although systemic treatment is favored to reduce the risk of relapse.

EAHP18-LYWS-375

Nodular pulmonary light chain deposition disease

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Case description: 33 year old man presenting with a left upper lobe lung mass. Radiologic examination shows no other adenopathy or lesions. Laboratory studies are normal, no evidence of an M protein by serum or urine electrophoresis.
Biopsy fixation details: Formalin-fixed, paraffin-embedded tissue.
Frozen tissue available: N/A
Details of microscopic findings: Well-circumscribed nodule of amorphous material with cracking artifact. This material is associated with foreign body giant cells and with several foci of ossification. Surrounding this material is a lymphoplasmacytic infiltrate composed of small, mature lymphocytes and plasma cells. There are no normal lymphoid structures.
Immunophenotype: The amorphous material is negative for Congo Red and its examination under polarized light shows no abnormal discoloration. Immunohistochemical stains for P component, Transthyretin, Amyloid A, Kappa or Lambda are also negative on the amorphous material. The lymphocytes are predominantly CD20 positive B-cells. The plasma cells are monotypic lambda.
Cytogenetics: N/A
Molecular studies: N/A
Proposed diagnosis: Nodular pulmonary light chain deposition disease associated with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).
Interesting feature(s) of submitted case: Nodular pulmonary light chain deposition disease is a rare entity with many features identical to those of pulmonary amyloid on routine examination. However, Congo Red stains, electron microscopy and immunohistochemistry tests show no evidence of amyloid deposits. This rare entity is often associated with marginal zone lymphoma or with autoimmune diseases. The clinical course of this entity is indolent, most cases do not require aggressive treatment. These cases have to be differentiated from the diffuse, cystic pulmonary light chain deposition disease, an aggressive disorder, often lethal, which requires lung transplantation.

EAHP18-LYWS-392

Simultaneous thyroid diffuse large B cell lymphoma transformed from extranodal marginal zone B-cell lymphoma and cervical lymph node classical Hodgkin lymphoma

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Case description: 50-year-old male with a long history of lymphocytic thyroiditis. He had been followed with annual ultrasounds and fine needle aspirations. This year ultrasound showed a left thyroid lobe nodule and left cervical lymphadenopathies not seen before. Fine needle aspiration was done from the left thyroid lobe and lymph nodes. The thyroid smears showed a monotonous population of predominantly small lymphocytes with scattered atypical large lymphocytes. The cervical lymph node aspirate showed numerous small lymphocytes with few large Reed-Sternberg like cells. Flow cytometry was done on both thyroid and lymph node samples. A polytipic population of B lymphocytes was found. Although the flow findings didn´t support the cytologic suspicion of lymphoma, a lymph node biopsy was requested. The case was discussed with the hematologist and it was decided to resect a lymph node and the thyroid. On gross examination, the thyroid showed multiple tan fleshy soft nodules.
Biopsy fixation details: the surgical specimens were fixed in formalin.
Frozen tissue available: No frozen tissue is available
Details of microscopic findings: The normal parenchyma of the thyroid was almost completely effaced by a diffuse proliferation of intermediate to large cell lymphocytes. Multiple aggregates of intermediate to large cell lymphocytes filling the lumens of thyroid follicles , “MALT balls” were seen. In only one block, a diffuse infiltrate of large cells with brisk mitotic activity was found. The lymph node sections show a monotonous population of small lymphocytes. Within this backgroud, there are several large lymphoid cells with prominent nucleoli and features suggestive of Reed Sternberg cells.

Immunophenotype: Thyroid: CD20 highlights the B lymphocytes present in folicular centers and the large atypical cells within thyroid acini. The germinal centers express bcl-6 and CD10 but are negative for bcl-2. The atypical intra-acinar lymphoid cells are negative for bcl-2, bcl-6, CD10 y MUM-1. The large lymphoid cells with brisk mitotic activity express CD20 and bcl-6 and are negative for bcl-2, CD10 and MUM-1. The ki 67 proliferative index was over 95%
Lymph node: The large neoplastic cells are CD30, CD15 and PAX5 (weak) positive, some large cells express CD20 (weak). These cells are negative for CD45 , BOB-1 and LMP1.

Cytogenetics: Not done

Molecular studies: Not done

Proposed diagnosis: Thyroid: diffuse large B cell lymphoma transformed from extranodal marginal zone B-cell lymphoma
Cervical lymph nodes: Hodgkin lymphoma, classical, lymphocyte rich

Interesting feature(s) of submitted case: Simultaneous presentation of transformed marginal thyroid lymphoma and lymph node Hodgkin lymphoma

EAHP18-LYWS-395

Liver mass in a patient with hepatitis C

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Case description: 64 years old male who presented to his local hospital with chest pain and minimal dyspnea. Past medical history includes hepatitis C (untreated), COPD, hypertension. The initial radiological work-up revealed right side pulmonary embolism and an approximately 9 cm mass in the right hepatic lobe. Subsequent positron emission tomography (PET) scanning showed an intensely hypermetabolic mass within the hepatic segment 4 and multiple metabolically active lymph nodes above and below the diaphragm (measuring up to 1.4 cm- 1.6 cm).
Initial laboratory work-up demonstrated Hepatitis C virus (HCV) RNA level of 89,884 IU/mL, and elevated lactate dehydrogenase (LDH) at 620 U/L, while the liver function tests were normal and HIV testing was negative.
Biopsy fixation details: The hepatic mass biopsy was fixed in 10% neutral buffered formalin.
Frozen tissue available: Not available
Details of microscopic findings: The biopsies demonstrate almost complete replacement of the liver parenchyma by a diffuse lymphoid infiltrate composed of monotonous sheets of medium-sized lymphocytes with round nuclei and frequent individual cell necrosis (Fig 1-3). Interspersed among these lymphocytes are macrophages with apoptotic debris which give a “starry-sky” appearance at low power magnification. Only small areas of residual hepatic parenchyma are seen at the edges of some of the core biopsies (Fig 1).
Immunophenotype: Immunohistochemistry results: The tumor cells are positive for CD45, CD20, PAX5, BCL6, CD43, MUM1, MYC, and negative for CD3, CD5, CyclinD1, BCL2, CD30, TDT, CD138, and cytokeratin AE1/AE3. Only very rare cells are weakly positive for CD10. EBV-encoded RNA (EBER) in-situ hybridization (ISH) is negative while ki67 shows a very high proliferative rate (nearly 100%).
Flow cytometry was not performed (fresh tissue not available).
Cytogenetics: Fluorescent in situ hybridization (FISH) studies performed on sections of the liver mass biopsies using Vysis dual color break-apart rearrangement probes for MYC, BCL2 and BCL6 genes demonstrate MYC rearrangement with no evidence of BCL2 or BCL6 rearrangements. Additional testing shows t(8;22) MYC/IGL fusion in 100% of the nuclei (Dual color double fusion strategy), with no evidence of MYC/IGH or MYC/IGK fusions.
Molecular studies: Not performed
Proposed diagnosis: Burkitt lymphoma
Interesting feature(s) of submitted case: Although Burkitt lymphoma often presents in extranodal sites, the liver involvement is very rarely encountered.
The concurrent hepatitis C is also interesting and raises the question of a potential pathogenic role of HCV, due to chronic antigenic stimulation.
In this case the tumor cells are mostly negative for CD10, feature that can be seen rarely in sporadic cases of Burkitt lymphoma (Kelemen et al, 2010).
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EAHP18-LYWS-407

The perils of steroid-treatment: a difficult classical Hodgkin's lymphoma case

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Case description: A 20 year old female presented with rapidly enlarging neck lymphadenopathy and rapidly progressive airway compression. On imaging, she was found to have a mediastinal mass. Two neck lymph node biopsies were undertaken 10 days apart and both showed necrotic material only. A third lymph node biopsy was received 6 weeks after the first biopsy and was also non-diagnostic. At this point the ENT surgeons provided additional information, namely that the "patient has received a few days' worth of steroid treatment, due to concerns about airway compression. In view of suspicious molecular findings and the clinical picture, mediastinal biopsy was undertaken, ultimately permitting a diagnosis of steroid-treated classical Hodgkin's lymphoma to be made. The patient subsequently responded very well to chemotherapy.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: First and second biopsy: Entirely necrotic.
Third biopsy: Cores of necrotic lymphoid tissue were received. On immunostaining the only cells that appeared to stain specifically were small CD3+ T-cells. No granulomas were seen. Special stains for mycobacteria and fungi were negative. Repeat biopsy was advised. Additional immunostains, undertaken retrospectively, identified a similar pleomorphic population to that in the fourth biopsy, although this largely necrotic population could not have been used for diagnosis.
Fourth biopsy: These biopsies comprised fibrotic mediastinum with entrapped thymus and some surfaces covered with reactive-looking mesothelial cells. There was no obvious necrosis. In places, there were small cystic structures within the thymus lined by respiratory type epithelium. The thymic epithelium appeared reactive in nature and it contained a population of small CD3+ T-cells with variable CD4 and CD8 expression and strong expression of CD2, CD5 and CD7, comprising the main cell type in the biopsy. These cells were TdT- and CD1a-. There were also scattered small B-cells, which did not show obvious pleomorphism or immunophenotypic abnormality (CD20+, CD79a+, pax-5+, myc-). A small number of pleomorphic cells were seen nestled among the T-cells.
Immunophenotype: The pleomorphic cells were weakly CD30+, Mum-1+, CD15-, weakly CD79a+, CD20-, Pax-5-, and EBV (EBER)-.
Cytogenetics: None
Molecular studies: Third biopsy: Monoclonal for IgH and IgK rearrangements in a polyclonal background; Fourth biopsy: polyclonal for IgH and IgK rearrangements.
Proposed diagnosis: Steroid-treated classical Hodgkin lymphoma
Interesting feature(s) of submitted case: This case demonstrates the difficulty associated with the diagnosis of classical Hodgkin's disease if corticosteroid therapy is instigated prior to diagnosis. It also demonstrates that, on occasions, B-cell clonality studies can be useful in the diagnosis of classical Hodgkin lymphoma.

EAHP18-LYWS-431

Multimodality diagnostics in an anterior mediastinal mass

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Case description: A 51 year old female patient presented in December 2011 with right supraclavicular lymphadenopathy and dyspnea. On PET-CT an anterior mediastinal mass and an enlarged right supraclavicular lymph node without further lymph node or organ involvement was noted. An incisional biopsy of the supraclavicular lymph node was performed. Complete staging, including a bone marrow trephine showed stage II disease. IPI score was determined as 2 and she was treated with 8 cycles of R-CHOP chemotherapy, followed by involved field radiotherapy. Complete remission was achieved and lasting (last follow-up December 2017).
Biopsy fixation details: 4% buffered formalin
Frozen tissue available: no
Details of microscopic findings: The incisional biopsy was of poor quality, precluding detailed morphological analysis. Diffuse infiltration of tumor cells between preexisting structures was noted. Fibrosis or nest-like compartmentalization was not present. In some areas, a blastic morphology could be recognized as well as clear cytoplasm. Morphology was not conclusive.
Immunophenotype: CD20, CD79a, CD30 positive
CD23 likely negative (artifacts)
EBER, CD15, CD3, CD5 negative
CD21 weakly positive
Cytogenetics: no
Molecular studies: Integrated molecular information in a single NGS assay to detect copy numbers, mutations and translocations from the FFPE material as developed in our lab:
Losses on chromosome 1, 3, 4q, 7p,10p12 14q31-32, 19p13 and 20q13.13-13.2. Gaines on chromosome 5p, 9p24.3-p23 and 20
Mutation analysis for 355 genes from the same assay shows a spectrum with high similarity to reported findings in PMBCL in contrast to DLBCL (see PPT information)
Combined information from mutation and copy number analysis adds additional PMBCL markers (e.g. PTPN1, associated with 20q13.13 loss)
Translocation analysis from the same assay shows an amplification of the PDL2 locus and a subclonal t(8;X) MYC-chrX translocation, and a t(1;2) Trim33-ERBB4 translocation
Proposed diagnosis: primary mediastinal B-cell lymphoma (PMBCL)
Interesting feature(s) of submitted case: The architecture and morphology were not characteristic and the immunofenotype was equivocal due to technical artifacts, precluding a definite diagnosis of PMBCL. The clinical presentation was suggestive, except for a relatively high age of the patient (51 years old).
Using a recently developed technique in our lab, we could retrieve integrated molecular information in a single assay from the FFPE material from this lymph node biopsy.
Typical gain of 9p24 with a superimposed amplification of the PDL2 locus only was detected, which is highly characteristic of PMBCL. A paucity of CNAs was noted, characteristic of PMBCL as well as a mutation spectrum with significant similarities to published data on PMBCL and not consistent with the spectrum seen in either GCB- or ABC-DLBCL.
Using this approach, we could collect objective arguments to support classification as primary mediastinal B-cell lymphoma despite poor quality of the biopsy sample. Especially in cases in which only small needle biopsies are available, which is often the case in mediastinal/thymic masses, this approach may be a value for diagnostic practice and support treatment choices.

EAHP18-LYWS-446

Large Primary Cutaneous Mantle Cell Lymphoma with Transformation into Pleomorphic Variant Mantle Cell Lymphoma: A Case Report from A Limited Resources Center

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Case description: A 37 year-old male with no significance past medical history was referred to our hospital with a rapidly growing ulcerated tumour on the upper area of right lower leg, clinically suspected sarcoma. On history taking, the tumour was present for about 4 months earlier. Physical examination showed an ulcerative fungating tumour, 12 cm in diameter, (figure 1A and B). CT scan of the tumour area revealed bone erosion and infiltration of surrounding muscle. No lymph node enlargement at any site of the body. Biopsy was performed and histopathology examination consistent with Mantle cell lymphoma. The patient received 2 cycle of RCHOP chemotherapy but showed no response, then he was treated by radiotherapy and showed complete response. He presented 3 months later with recurrence tumour in the same area (figure 2) and also right inguinal lymph node enlargement. Biopsy was performed at the site of primary tumor and inguinal lymph node. Histopathology examination of both specimens consistent with pleomorphic variant mantle cell lymphoma.
Biopsy fixation details: Formalin-fixed paraffin embedded Tissue
Frozen tissue available: frozen tissue was not available
Details of microscopic findings: First biopsy : The specimen features a diffuse lymphomatous infiltrate featuring small to medium sized lymphocytes with slightly condensed chromatin, irregular nuclear contours and inconspicuous nucleoli. Hyalinized small vessels were markedly seen. Mitosis were plenty. Large areas of necrosis were noted. Trabecular pattern and pseudorosette formation were seen probably due to fixation and processing artifact (figure 3A-C)
Biopsy from recurrent tumor and lymph node : The specimen showed a necrotic tumour featuring sheets of medium to large lymphoid cells with round to slightly irregular nuclear contours, vesicular chromatin and prominent central nucleoli. There was moderate nuclear pleomorphism and frequent mitoses were noted. Hyalinized small vessels were markedly seen. (figure 4)
Immunophenotype: First biopsy : Immunohistochemistry showed expression of CD20 and a high proliferation fraction of up to 80% with Ki67 staining, in keeping an aggressive B-cell lymphoma. Staining for CD3 was negative. There was expression of MUM1 but not MyoD1, pancytokeratin were also negative. Additional staining for cyclin D1 shows extensive nuclear expression. (figure 5)
Biopsy from recurrent tumor and lymph node: Immunohistochemistry confirmed the B-cell lineage of the lymphomatous population, being positive for PAX5, accompanied by a minor population of CD3+ reactive T-cells. Neoplastic cells displayed a high proliferation fraction of >90%. There was focal expression of CD10 and strong expression of c-myc (90%) and bcl2 (>90%). (figure 6)
This result showed a large B-cell lymphoma with high level expression of c-myc and bcl2. The morphology was slightly different from the first biopsy. However, given the earlier diagnosis of mantle cell lymphoma, this most likely represents relapse with transformation to pleomorphic variant mantle cell lymphoma.
Cytogenetics: Not available
Molecular studies: Not available
Proposed diagnosis: Primary Cutaneous Mantle Cell Lymphoma with Transformation into Pleomorphic Variant Mantle Cell Lymphoma
Interesting feature(s) of submitted case: This is a rare case with clinical appearance of the tumour resembling sarcoma. This case also showed large area of necrosis, mantle cell lymphoma with large area of necrosis is uncommon. Fixation and processing artifact made the morphology of this case more confusing

EAHP18-LYWS-465

An extranodal presentation of EBV+ classical Hodgkin Lymphoma, lymhpocyte deplete subtype

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Case description: A 61 year old male presented with a 4 month history of peri-anal ulceration clinically suspicious of Crohn's disease. An excision specimen of the anal ulcer was subsequently submitted (slides submitted). On the advice of the reporting pathologist, a staging computed tomography scan was performed, showing inguinal lymphadenopathy. A core biopsy of the inguinal lymph node was perfomed (not submitted owing to tissue paucity). There was no significant past medical history or history of iatrogenic immunosuppression.
Biopsy fixation details: Neutral buffered formalin.
Frozen tissue available: Not performed.
Details of microscopic findings: The excision specimen showed ulcerated squamous lined tissue with an extensive mixed infiltrate of small lymphocytes, neutrophils, histiocytes and large lymphoid blasts with prominent nucleoli. Some of the blasts showed Hodgkin-like features. The blasts formed confluent nests in areas. The infiltrate penetrated the deep tissue extensively and showed no circumscription.
The subsequent lymph node core biopsy showed an effaced lymph node with variable fibrosis and a mixed infiltrate composed of small lymphoid cells, eosinophils, histiocytes and large lymphoid blasts including Hodgkin-like and Reed-Sternberg-like cells.
Immunophenotype: The phenotype of the blastic cells in the ulcer excision was as follows: PAX5+(weak), CD79a+/-, CD20-, CD45-, CD3-, AE1/AE3-, CD30+, ALK1-, CD8-, CD4-, CD2-, CD5-, CD7-, CD21-, CD23-, CD25+, CD43+/-, BOB10, OCT2-, CAM5.2-, Granzyme-, TIA1-, Perforin-, EMA-.

The blastic cells within the lymph node core showed the same immunophenotype.
Cytogenetics: Not performed.
Molecular studies: EBER in situ hybridisation showed conspicuous positive blasts in the ulcer and core biopsy.

PCR:
B-cell clonality studies on the lymph node core showed a weak B-cell clone with background polyclonality. T-cell and B-cell clonality studies on the ulcer specimen showed polyclonality.
T-cell clonality studies in the lymph node core failed due to poor DNA quality.
Proposed diagnosis: EBV+ classical Hodgkin lymphoma, lymphocyte deplete subtype.
Interesting feature(s) of submitted case: Extranodal presentation of EBV+ classical Hodgkin Lymphoma is rare. This case presented as anal ulceration thus clinically mimicking Crohn's disease. The excision specimen of the anal ulcer showed an EBV+ B-cell lymphoproliferation, the differential diagnosis of which included EBV+ mucocutaneous ulcer, EBV+ classical Hodgkin lymphoma and chronic inflammation associated diffuse large B-cell lymphoma. The absence of CD20 expression, the extensive deep involvement of the tissue, and the confluent nests of cells favoured classical Hodgkin lymphoma.
Inguinal lymphadenopathy detected on a staging CT scan yielded a core biopsy which showed similar features in the lymph node, thus confirming the diagnosis of classical Hodgkin lymphoma.

EAHP18-LYWS-470

Concurrent Rosai Dorfman disease of the testis and marginal zone lymphoma of salivary gland

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Case description: A 51 year old male with endocrinological antecedents and a history of congenital complement deficiency with lupus-like illness, presented in 2014 with multiple lymphadenopathies, swelling of the parotid gland and bilateral testicular swelling, clinically suspicious for lymphoma. Patient had no B-symptoms and EBV viral load was negative.
Incisional biopsy of the parotid gland (B-1722064) and radical orchidectomy (B-1722078) were performed.
Biopsy fixation details: BF **Frozen tissue available:** y
Details of microscopic findings: Parotid:
Section through tissue containing a small-sized lymphoproliferative population obliterating the parotid glandular parenchyma and infiltrating in the remaining ductular structures (so called lymphoepithelial lesions). The cells are small and monotonous with cleaved nuclei and dens nuclear chromatine and small rim of pale cytoplasma. There is no large cell transformation and no necrosis. Throughout the sample we also recognize reactive germinal centers. Morphologically suspect for extranodal marginal zone lymphoma.
Testis:
Macroscopy: 4.8 x 3.2 x 3 cm. There is no clearly delineated tumoral lesion, but the testicular parenchyma in the center is paler and has a more firm consistency than the peripheral rim of 2mm normal appearing parenchyma.
Microscopy: Centrally in the testis, the parenchyma shows an extensive atrophy of the seminiferous tubuli, with Sertoli-cell-only. There is a very prominent intertubular and diffuse interstitial infiltrate consisting of large cells with abundant pale eosinophilic cytoplasm. The cells show abundant emperipolesis (of lymphocytes and plasma cells), but show no increased mitotic activity. The do not contain Michaelis-Gutmann bodies (as seen in malakoplakia). This histiocytic population is intermixed with small lymphocytes (often in small aggregates), eosinophils, and sparse plasma cells. The histiocytic infiltrate also extends partially in the epididymis. At the periphery there is still preserved spermatogenesis.
Immunophenotype: Parotid:
The B-cell population that extends from the marginal zone of the remaining reactive germinal centers, expresses CD20 and Bcl2 and has a very low proliferative activity (<5%), but in contrast to the remaining germinal centers does not express Bcl6 or CD10. There is no expression of LEF1, CyclinD1, CD5, CD23 or CD21 in the B-cell population. The CD23 and CD21 stains however illustrate residual FDC networks.
Cytokeratin stain and CD20 stains illustrate extensive infiltration of B-cells in the remaining ducts, so called lymphoepithelial lesions.
Testis:
The diffusely infiltrating histiocytic population expresses CD68/PGM1 and S100. The latter also nicely illustrates the emperipolesis. The histiocytes do not express CD1a. B-cells are sparse.
Cytogenetics: -
Molecular studies:
Parotid:
PCR confirms B-cell clonality
FISH: normal MALT1/18q21 and BCL6/3q27
Testis:
PCR no B-cell clonality, no BRAF mutation
Proposed diagnosis: Concurrent Rosai Dorfman disease of the testis and marginal zone lymphoma of salivary gland
Interesting feature(s) of submitted case:
Rosai Dorfman disease of the testis is very rare (only 11 cases in literature). We have 2 cases in our archive (1 was presented here). Intriguingly 4/13 show association with B-NHL!
Review of literature:
31 cases suggest association between RDD and lymphoma:
–Hodgkin (10); NHL (6 DLBCL, 6 MALT/MZL, 3 FL, 2 CLL/SLL, 1 ALCL, 1 T-NHL, 2 NOS)
–18/31 happen concurrent (12 of which in the same organ);
–7/31 RDD occurs after NHL : mean of 8,1 yr interval (range 5-12y)
–6/31 NHL occurs after RDD : mean of 3,5 yr interval (range 0,8-8y)
Note: spontaneous regression of lesions after orchidectomy.

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Massive subcutaneous swellings in LPL/Waldenström patient due to amyloidoma.

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Case description: A 71 year old male with a history of chronic inflammatory demyelinating polyneuropathy, was diagnosed in 2003 with a monoclonal B-cell population (IgM kappa), for which he was treated with chlorambucil. Over the years there was a steady increase of IgM and in 8-2017 the diagnosis of Waldenström macroglobulinaemia (IPSSWM1) was made and he was treated with anti-CD20 in combination with bendamustin. A bone marrow trephine was performed (B-1885021: see images). He developed multiple subcutaneous masses (cervical, axillary, mediastinal, hilar, periportal), that were firm, hard to mobilize. There was no hepatosplenomegaly.
Although the blood values corrected under the treatment, the masses did not respond and a biopsy was taken to exclude large cell transformation.

Biopsy fixation details: BF
Frozen tissue available: y
Details of microscopic findings: The bone marrow trephine showed only subtle involvement by a lymphoplasmacytic infiltrate with sparse Dutcher bodies.
The masses were biopsied twice, but none of the masses were recognized as lymph nodes:
B-1892536
Showed fibroadipose tissue with deposition of eosinophilic hyaline material in the connective tissue, surrounding the adipocytes and in the wall of the blood vessels.
B-1894693
A second biopy of another, larger mass showed similar deposition of eosinophilic hyaline material in the connective tissue. There was an interstitial infiltrate of morphologically non-atypical plasmacells and histiocytes (some of which multinuclear) interspersed between the hyaline material. No large cells.
Immunophenotype: The infiltrate in the bone marrow was partially CD20, partially CD138 positive and expressed IgM. Congored stain showed amyloid deposition in the periostal connective tissue and blood vessel walls.
Large parts, although not all, of the eosinophilic deposits stained on the Congored special stain and show birefringent green color on polarization, proving its amyloid structure.
The plasma cells present between the eosinophilic deposits were kappa light chain restricted, as were the lights chains that were detected in the blood. There were no B-cells present in the samples.
Cytogenetics: -
Molecular studies: Presence of c.794T>C (p.(L265P)) mutation in the MYD88 gene in 28.00% of cells in the bone marrow
Proposed diagnosis: Amyloidoma occuring in a patient with lymphoplasmacytic lymphoma/Waldenström.
The plasma cells present in the subcutaneous masses were interpreted as a residual localisation of the LPL, but due to the massive deposition of amyloid, the lymph nodes did not shrink after therapy.
Interesting feature(s) of submitted case: ·The massive "lymphadenopathy" in this LPL/WM patient was not due to nodal involvement by lymphoma or large cell transformation but due to prominent amyloid deposition, aka amyloidoma
·Amyloidoma is rarely reported in LPL/WM
·Kappa restricted plasmacell population in between amyloid to be interpreted as residual plasma cell component of LPL

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Perforated gastic ulcer: misdiagnosis of a B cell lymphoma with Myc rearrangment

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Case description: In 2013, a 86 year old woman was admitted to the emergency department for acute abdominal pain. She has been followed for a medically treated gastric peptic ulcer.
Abdominal CT scann evidenced a gastric perforation, a severe peritonitis and a suspected underlying evolutionary process. Enlarged coelio-mesenteric lymph nodes were associated with a heterogeneous splenomegaly.
Partial gastrectomy was performed: a deep infiltrating tumor (6,5cmx 4,5cm) was evidenced.

The patient was then treated with 7 courses of chemotherapy (Rituximab and cytarabine.
In 2016, a deep subcutaneous nodule of the back was discovered
Biopsy fixation details: buffered formalin
Frozen tissue available: No frozen tissu available
Details of microscopic findings: 1) gastric lesion
small to medium size crowded lymphoma cells were destroying the gastric wall.
Around the perforation, the mucosa was invaded. All the lymph nodes of the the lesser curvature of the stomach were involved.
2) Subcutaneous nodule:
packed small to medium size lymphocytes invasive the adjacent adipose tissue. Nuclei have a fine chromatin and quite numerous mitosis and picnose beaches without necrosis
Immunophenotype: 1) Gastric lesion:
CD20+, CD79A+, Bcl2+, CD5-, CD10-, CD23-, Cycline D1-, CD43-, Myc + (90%), Ki67 5%.
Blood flow cytometric analysis :
lymphocytes were B, CD20+, lambda +, CD19+, CD 22+, CD 79B+, FNC7+, CD 81+, 5-, CD 23-, CD 10-, CD 43-, CD 200-. Matutes score : 0.
2) Subcutaneous nodule
CD20+, CD79A+, Bcl2+, CD5-, faint CD10+, CD23-, Cycline D1 (very faint immunostaining of about 40% of the cells), CD43-, Bcl6 less than 10% of the cells,Ki67 40% of the tumoral cells, Myc 90% of the cells, HGAL +, Sox11-, MUM1-
flow cytometric analysis : lymphocytes were B, CD20+, lambda +, CD19+, CD 22+, CD 79B+, FNC7+, CD 81+, 5-, CD 23-, partial CD 10+ , CD 43-, CD 200-.
Cytogenetics: 1) Interphasic fluorescent in situ hybridization on gastric:
- no rearrangement of BCL2 18q21, BCL6 3q27, MALT 18q21.
- Rearrangement of Myc 8q24.
- Not rearrangement of Bcl1 -11q13
2) Interphasic fluorescent in situ hybridization on subcutaneous lesion :
- no rearrangement of BCL2 18q21, BCL6 3q27, MALT 18q21.
- Rearrangement of Myc 8q24.
- Not significant rearrangement of Bcl1 -11q13 (in less than 10% of the cells).
Molecular studies: BIRC3
9
c.1663_1666delAGAA
p.Arg555Hisfs*12

MYC
2
c.135C>G
p.Asn45Lys
variants found in gastric lymphoma and gastric lymph nodes and in subcutaneous nodule
ATM
61
c.8788T>C

p.Cys2930Arg

Variant found only in subcutaneous nodule
2
c.104A>T
p.Gln35Leu
Proposed diagnosis: Germinal center lymphoma with Myc 8q24 rearrangement
Interesting feature(s) of submitted case: Interesting feature(s) of submitted case: A lymphoma with unusual clinical presentation and phenotype

EAHP18-LYWS-501

A sheep in wolf's clothing: follicular dendritic cell sarcoma masquerading as diffuse large B-cell lymphoma

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Case description: We received small axillary core biopsies from a 63 year old lady with an ill defined, diffuse, spreading subcutaneous/ deep soft tissue mass, involving a region extending between the left neck and left axilla. She had been diagnosed elsewhere with diffuse large B-cell lymphoma in a single left level III neck lymph node 8 years previously and treated with CHOP-R, allogeneic stem cell transplant and local radiotherapy, with apparent complete remission. 4 years later gradual recrudescence of the neck mass began, with subsequent slow spread in continuity into the axilla. No bone marrow involvement was demonstrated at any point. Review of all previous biopsies showed no definite evidence of previous B-cell lymphoma. Follicular dendritic cell (FDC) sarcoma was the best unifying diagnosis.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: 2017 biopsy: cores of lymphoid tissue with widespread infiltration by large sheets of pleomorphic, occasionally mutlinucleate cells, with prominent nucleoli, abundant eosinophilic cytoplasm and fequent mitoses. Numerous plasma cells and scattered lymphoid cells surrounded the pleomorphic cells.
2009 biopsy: A very large mass of lymphoid tissue, in which no sinuses or obvious capsular structure were seen, although there was fibrosis around the mass. The mass comprised wide skeins and sheets of large, moderately pleomorphic, oval/ elongated cells some with clear cytoplasm. Adjacent small lymph nodes appeared reactive. Biopsies in the intervening period between 2009 and 2017 showed similar features.
Immunophenotype: 2017 biopsy: PAX8+, PAX5+ (weak), CD117+, vimentin+, CD99+. Focal weak EMA+, WT-1+, focal calretinin+. Weak HHV8+ (possibly non-specific). MIB-1 proliferation index 60%. CD45-, CD20-, CD3-, CD5-, CD68PGM1-, CD30-, AE1/3-, CD138-, CD34-, ERG-, actin-, desmin-, calponin B-, synaptophysin-, S100-, SOX10-, p63-, CD99-.
2009 biopsy: CD45-/weak+, CD3-, mainly CD20- (10-20%+), largely CD79a-, Mum-1+ (occasional cells), largely pax-5- (10-20% weak+), OCT2+ (10%+), largely Bob-1- (except occasional cells), largely CD10-, weakly bcl6+, LMO2+ (occasional cells), largely stathmin-1-, bcl-2-, weakly CD68KP1/PGM1+ , Factor 13a- , strongly D2-40+, CD1a-, EMA+/-, CD23-, largely CD21- (occasional weak+), MSA-, desmin-, weakly PAX-8+, AE1/3-, 34BE12-, BRAF V600E-mut-spec+, weak nuclear HHV8+, EBV(EBER)-, CD138-, CD31-, ERG-, CD34-, S100-, CD30-, HER-2 langerin- and WT1-. Mib1 proliferation index 10 - 20%. Kappa/ lambda IHC+ on a small proportion, likely indicating Fc receptor-bound immunoglobulin.
Cytogenetics: EWSR1 dual colour break apart rearrangement probe showed unrearranged EWSR1, but detected one to two extra copies. As 60% of cases of angiomatoid fibrous histiocytoma carry a rearrangement of EWSR1, this failed to confirm a diagnosis of angiomatoid fibrous histiocytoma.
Molecular studies: All specimens tested were polyclonal for IGH, IGK, IGL, TRG and TRB gene rearrangements.
Proposed diagnosis: Follicular dendritic cell sarcoma

Interesting feature(s) of submitted case: (1) Large activated B-cells in a follicular dendritic cell sarcoma may raise concerns about B-cell lymphoma; (2) close apposition of B-cells and follicular dendritic cell membranes in FDC sarcoma make it difficult to determine which cell type expresses particular antigens; (3) FDC sarcoma may show loss of conventional FDC markers (CD21 and CD23), while expressing markers more usually associated with B-lymphocytes, such as Pax-5 and (4) adsorbed antibody attached to FDCs can give the impression of immunoglobulin light chain expression.

EAHP18-LYWS-509

Hepatosplenic T-cell lymphoma in a 74-year-old man

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Case description: A 74-year-old man with a history of coronary artery disease, type 2 diabetes, pemphigus vulgaris, and prior splenectomy due to childhood traumatic injury, presented with acute onset fever and hypoxemia. No lymphadenopathy or hepatomegaly was seen. He was initially treated with empiric antibiotics for presumed pneumonia without improvement and subsequently developed liver failure (rising transaminases, alkaline phosphatase, bilirubin). Upon transfer to the ICU, he was continually treated with steroids for possible interstitial lung disease (diffuse bilateral ground-glass opacities on CT), possible myositis (profound weakness, elevated aldolase) and/or possible autoimmune hepatitis. However, his liver function tests continued to worsen despite high-dose steroids. CBC at the time of bone marrow biopsy: WBC: 18.10 K/uL, including 16.13K/uL neutrophils and 4.9 K/uL lymphocytes (ref 1.0-4.8 K/uL); HGB: 9.7 g/dL; PLT: 111 K/uL.
Biopsy fixation details: Formalin-fixed, paraffin-embedded tissue section
Frozen tissue available: None
Details of microscopic findings: Review of the core biopsy shows portal and periportal aggregates of lymphocytes with scant-to-moderate pale cytoplasm, irregular nuclear contours, and vesicular chromatin. Linear arrays of neoplastic cells are also present, consistent with extensive sinusoidal infiltration. The lymphoid infiltrate is associated with focal hepatocyte injury. A trichrome stain shows no convincing evidence for fibrosing liver disease. Iron stain shows no stainable iron and PASD stain shows no PASD positive globules. Stains for spirochetes, CMV, Hepatitis B virus (Hep B surface and Hep B core), and HSV are negative. In-situ hybridization for Epstein-Barr virus encoded RNA (EBER) is negative.
Immunophenotype: Immunohistochemical stains show that neoplastic cells are CD3+ CD2+ CD7+ CD56+ CD4- CD5- T cells that are mostly negative for CD8 (CD8-/+). The neoplastic cells express TCR-gamma/delta and are negative for beta-F1. Most neoplastic cells are negative for perforin and granzyme, with a small subset of faintly positive cells in focal aggregates. A small subset of cells show faint staining for CD25. There are rare scattered admixed CD20+ B cells.
Cytogenetics: None
Molecular studies: None
Proposed diagnosis: Hepatosplenic T-cell lymphoma
Interesting feature(s) of submitted case: The combination of morphology together with the immunophenotype of the atypical T-cells (CD3+ CD4- CD5- TCR-gamma/delta+ CD56+) are consistent with hepatosplenic T-cell lymphoma (HSTCL). Unfortunately, given the patient's deteriorating clinical status, he was not able to receive any chemotherapy and died 11 days after diagnosis. Correlation with FISH for isochromosome 7q, which is present in many cases of HSTCL, was not performed in this context.

Interestingly, this patient's age is unusual for HSTCL, which typically occurs in young adults (median age 35). However, the presentation of disease is otherwise quite consistent with HSTCL. The overall immunophenotype and clinical presentation (absence of lymphocytosis and aggressive clinical behavior) distinguishes this from alternative diagnostic considerations, such as T-cell large granular lymphocytic leukemia (T-LGL).

EAHP18-LYWS-518

Diffuse large B-cell lymphoma of the breast associated with clonally unrelated IgG4-positive plasma proliferation in ipsilateral axillary lymph node in a patient with AAPOX syndrome

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Case description: 51-year-old woman presented 2016 with multiple subcutaneous nodules on trunk. On physical examination, a lump was found in the right breast, with enlarged right axillary lymph nodes. Previous medical history: recurrent swelling of the eyelids/periorbital regions, trigeminal neuropathy, nasal polyps, cataract and asthma.
Peripheral blood 2016: Hgb 126 g/L, WBC 5 x10(9)/L, PLT 273 x10(9)/L. MCV 92 fL. Mild hypoalbuminemia, increased IgG background but no clonal peaks.
Subcutaneous lump from right breast was first punctured (FNAB) and later removed, alongside with right axillary lymph node (T10502-16, submitted) due to suspicion of malignancy.
Bone marrow biopsy (2016, not submitted) showed 40% cellularity, no focal lesions. Flow cytometry BM: reactive lymphocyte immune profile.
Biopsy fixation details: Zinc formalin
Frozen tissue available: Yes
Details of microscopic findings: Tumour R breast (T10502-16, 1A): dermal/subcutaneous large cell infiltration with pleomorphism, nucleoli, lobated nuclei. Admixed dispersed small lymphocytes, histiocytes, few plasma cells. Lesion is delineated on one side, with lymphohistiocytic panniculitis-like inflammatory infiltrate on the other side.
R axillary lymph node (T10502-16, 2B): 5 cm large, multiple lymphatic follicles and fibrosis separating tissue in nodules. No CHL diagnostic cells. In peri-and interfollicular follicular areas prominent plasma cell infiltration.
Immunophenotype: Tumour of R breast
Large cells: CD45+, CD20+, PAX5+, MIB1 over 90%, c-cmyc+, CD38-, HHV8-, CD138-, CD30-, MUM1-(20%), CD10-, p53 partly +(40% dim), bcl6+, bcl2-, lambda+, cytokeratin-, oestrogen receptor -.
Small cells (surrounding large cell aggregate): mixture of T-cells and histiocytoid cells (CD68+ S100+), few B-cells, almost no plasma cells.
Flow cytometry: only 4% mononuclear cells including 2.8% T-cells (CD4/CD8=1.6), 0.1% NK-cells, max. 0.1% B-cells 20+.
R axillary lymph node
Small lymphocytes: mixture of T- and B-cells, single small EBER+ cells, HHV8-.
Plasma cells: CD138+, CD38+, PAX5 dim, EBER-, HHV8-, CD20-, p53-, CCND1-, kappa+, MIB1 30-40%, CD56-, IgG+, IgG4+ (almost 90% of all IgG+).
Flow cytometry: 81% mononuclear cells including 46% T-cells (CD4/CD8=9.3), 0.3% NK-cells, 32% polyclonal B-cells, 1.8% plasma cells.
Cytogenetics: Not studied.
Molecular studies: FISH on R breast tumour – negative for C-MYC rearrangement using break apart probe and fusion probe for t(8;14).
Proposed diagnosis: Extranodal infiltration of diffuse large B-cell lymphoma, GC-type, associated with nodal proliferation of monoclonal IgG4-expressing plasma cells in a patient with the AAPOX syndrome.

Interesting feature(s) of submitted case: The patient was first given clinical diagnosis of the AAPOX syndrome. This entity belongs to the spectrum of non-Langerhans type histiocytoses with granulomatous infiltration of periorbital areas. No underlying clonal marker was identified yet in AAPOX, which shows however a strong link to IgG4-related systemic disease. Coexistence of the latter with lymphoma or carcinoma has been described but there are no reports on association of AAPOX with malignancies.
In the presented patient, extranodal lambda-clonal DLBCL infiltration coexisted with a nodal kappa-clonal proliferation of IgG4-expressing plasma cells, which seemed to be the first manifestation of the possible IgG4-related disease. Interestingly, both lesions are not clonally related, and seem to represent two separate diseases. Malignant potential of the clonal plasma cell proliferation is difficult to assess.
The patient received 6x R-CHOP, thereafter periocular and cheek lesions regressed.

EAHP18-LYWS-568

EBV+/CD4+ T cell lymphoma of extranodal sites

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Case description: A 55-year old Korean female, admitted with a two months history of fever and abdominal pain. Initially, she had fever, dysuria and flank pain and was treated for acute pyelonephritis in the outside hospital. During the fever workup, computated tomography revealed multiple ill-defined hazy mesenteric nodules and prominent lymph nodes throughout the entire mesentery that were suggestive of mesenteric panniculitis, and mildly edematous wall thickening in the terminal and distal ileum. A few small lymph nodes with suspicious perinodal infiltrations were also found in the neck. In the colonoscopy, there were multiple ovoid ulcers involving from terminal ileum to rectum. Biopsies of the cervical, mesenteric nodes and colon were performed but were diagnosed non-specific inflammation.
The patient received empirical steroid and antibiotic therapy under the putative diagnosis of inflammatory bowel disease. Fever and abdominal pain subsided at first but the patient occasionally experienced wax and wane patterned fever for 1 year despite the treatment. In the follow up imaging studies, cervical lymphadenopathy progressed. For re-evaluation, lymph node biopsy and subsequent excision were done.
Biopsy fixation details: Formalin-fixed, paraffin-embedded sections
Frozen tissue available: Unavailable.
Details of microscopic findings: An excisional biopsy from the right cervical area revealed a diffuse proliferation of lymphoid cells involving fat. At low power, lymphoid cells are forming vague nodular, ovoid lesion without capsule and there is prominent necrosis. The tumors cells are small sized with irregularly-folded, angulated nuclei and inconspicuous nucleoli. Some cells have a moderate amount of pale cytoplasm. A few plasma cells and eosinophils are interspersed. Retrograde review of the mesenteric tissue also shows similar morphologic findings with perivascular cuffing of atypical lymphoid cells.
Immunophenotype: Small, atypical lymphoid cells are positive for CD3, CD5, CD4, EBER (EBV) by ISH. Ki-67 stain shows markedly increased proliferation index (~50%). Tumor cells are negative for CD20, CD8 and CD56a. Granzyme B is positively stained in some lymphoid cells but whether they are EBV+ cells is not clear.
Cytogenetics: Unavailable.
Molecular studies: Pending TCR gene rearrangement study results.
Proposed diagnosis: EBV+, CD4+ peripheral T cell lymphoma.
Interesting feature(s) of submitted case: The morphologic features of this case are similar to extranodal NK/T-cell lymphoma of nasal type (NKTL). However, immunophenotype is not typical. Differential diagnosis includes CD56-negative NKTL, T cell type NKTL and peripheral T-cell lymphoma (PTCL). In T cell type NKTL, neoplastic cells are cytotoxic T cells. Tumor cell are clearly CD4+/CD8+/EBV+ in this case, with equivocal cytotoxic granule expression. These features are not usual for the CD56-negative NKTL nor T cell type NKTL. However, association of peripheral T cell lymphoma with EBV is not well described.
This case has interesting characteristics that is hard to defined in a established diagnostic entity and shows a new spectrum of EBV associated lymphoma.

LYMPHOMA WORKSHOP SESSION 6

Extranodal lymphoproliferative disorders, not site specific

Chairs: A. Traverse-Glehen, M. Ponzoni

EAHP18-LYWS-500

Intravascular Large B-cell Lymphoma localized to skin

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Case description: A 68 y/o man, with a past history of polio and poor mobility was admitted in February 2016 with bilateral leg cellulitis, bilateral pulmonary embolism and acute kidney failure secondary to diuretic treatment. Despite multiple courses of antibiotics he continued to spike temperatures which eventually settled with steroids. An ulcerated haemangioma was resected from his left hip. Poor mobility was found to be due to a combination of issues including sensory neuropathy. After 7 months, the patient was discharged. He was readmitted 11 months later with bilateral swollen painful red thighs including indurated plaques. An initial skin biopsy from thigh revealed a panniculitis rich in plasma cells which were found to be kappa restricted. Investigations for myeloma, including protein electrophoresis and marrow examination, were negative. In view of the persistence of the rash, a second deep skin biopsy was taken.
Biopsy fixation details: 10% buffered formalin.
Frozen tissue available: No.
Details of microscopic findings: Normal epidermis and dermis. There is a large blast cell infiltrate exclusively within capillary channels within the subcutaneous tissue. Plasma cells were not present on this occasion
Immunophenotype: Positive: CD20, CD5, Bcl6, IRF4, Bcl2, MYC protein(70%).
Negative: CD2, CD3, CD10, CD30, CD138, CyclinD1, CD56, EBV ISH.
The Ki 67 proliferation rate is 90%.
Cytogenetics: Not available
Molecular studies: FISH for MYC rearrangement(breakapart probes) was negative.
Proposed diagnosis: Intravascular large B-cell lymhoma localised to skin
Interesting feature(s) of submitted case: Review of the excision biopsy of haemangioma taken 20 months prior to the final diagnostic biopsy revealed focal involvement by intravascular large B-cell lymphoma. The lymphoma was likely the cause of much of the patient's cutaneous problems with recurrent antibiotic resistant "cellulitis" and also PUO which responded to steroids. A CT and PET scan showed no evidence of lymphadenopathy or organomegaly. There was diffuse increased PET activity within the marrow. Immunostaining for CD20, PAX5 and CD79a performed on a poor quality trephine biopsy however showed no evidence of involvement by lymphoma. The condition has remained confined to skin for almost 2 years. The explanation for the finding of kappa restricted plasma cells in the first skin biopsy during the second admission is unclear. Is it possible that this could represent a differentiated extravascular component in chronically inflamed tissue.

EAHP18-LYWS-175

Indolent "prodromal" phase of extranodal NK/T-cell lymphoma, nasal type with subsequent skin involvement

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Case description: The patient is a 62-year-old male with pansinusitis, status post nasal and sinus surgeries in 2006, 2008 and 2015, who presented in May 2017 with skin lesions on his arms and legs. The lesions waxed and waned over several months with no response to antibiotic therapy. A 4 cm erythematous, firm plaque with central erosion on the right calf was biopsied in June 2017 and showed an extranodal NK/T-cell lymphoma, nasal type (ENKTL) (Biopsy #1). A whole body PET/CT scan showed no abnormal metabolic activity and a CT scan of the sinuses showed no obvious masses or destructive lesions. Re-review of bilateral nasal biopsies from March 2015 showed an abnormal EBV+ NK/T-cell infiltrate with a phenotype similar to the biopsy from the right calf (Biopsy #2). The patient received radiation therapy to the right calf lesion, but after a new skin lesion arose on the left lower leg in September 2017 he began oral methotrexate (20 mg/week). His methotrexate was increased to 30 mg/week in October 2017 when new skin lesions developed on the left leg and left forearm. As of December 2017, the patient's skin lesions have regressed and no new lesions have developed. A repeat whole body PET/CT showed no evidence of malignancy.
Biopsy fixation details: Formalin
Frozen tissue available: N/A
Details of microscopic findings: Biopsy #1 (2017): There is a dermal-based, superficial and deep, perivascular and periadnexal infiltrate composed of pleomorphic, intermediate-sized lymphoid cells with often irregular nuclear contours and occasional nucleoli. Epidermotropism is not identified. Biopsy #2 (2015, submitted slides): There is a patchy mucosal infiltrate composed of mostly small lymphoid cells with round to more irregular nuclear contours and condensed chromatin admixed with a variable number of eosinophils and plasma cells.
Immunophenotype: Biopsy #1: The infiltrate is positive for CD3, CD2, CD7, CD56, TIA1, Granzyme B, and EBER, has variable staining for CD30, but is negative for CD5, CD4, CD8, Beta F1, Delta TCR, CD57, PD1, CXCL13, ALK1, and CD25. The Ki-67 proliferative index is >50% in most areas. Biopsy #2: The infiltrate has a similar phenotype to that in Biopsy #1. However, the Ki-67 proliferative index is <10%.
Cytogenetics: N/A
Molecular studies: Biopsy #1: T-cell clonality is negative, but limited to BIOMED-2 primer sets TCRB B and C, and TCRG A (weak or no amplification with TCRB A and TCRG B primer sets).
Proposed diagnosis: Extranodal NK/T-cell lymphoma, nasal type with an indolent (at least 2 year) clinical course and subsequent skin involvement demonstrating histologic/immunohistologic progression.
Interesting feature(s) of submitted case: This case illustrates an ENKTL with an unusual indolent clinical course, as recognized on retrospective review of a nasal biopsy that had been diagnosed as a chronic inflammatory process in 2015. In 2017, however, he developed more aggressive-appearing cutaneous lesions with a much higher proliferative fraction, which required radiation and methotrexate therapy. This indolent clinical course is very unusual, as most ENKTL are highly aggressive. Whether the EBV+ NK/T-cell infiltrate in the nasal biopsy from 2015, which has much less cytologic atypia than that in the skin biopsy, could represent a precursor lesion to the subsequent ENKTL is uncertain. We are aware of several other cases of ENKTL with an indolent clinical course that either persisted or subsequently became an obvious overt aggressive neoplasm. A similar phenomenon has been described, for example, with T-cell prolymphocytic leukemia, an aggressive neoplasm that may have an indolent prodromal phase in some patients (Br J Haematol 1998;103:488-94).

EAHP18-LYWS-487

Plasma cell neoplasm of the testis revealing multiple myeloma.

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Case description: A 58-year-old HIV-negative patient presented in 04/2015 with painless enlargement of the right testis and night sweats for 2-3 months. Ultrasonography showed an enlarged heterogeneous and hyperemic right testis (68ml), suspicious for lymphoma. A right orchidectomy was performed (**submitted slide**). Additional work-up showed an IgA-Lambda monoclonal gammapathy (51.9mg/l) and bone marrow infiltration by 20-30% of IgA-Lambda plasma cells. PET-CT showed no bone lesions and the final staging was ISS-I, Salmon-Durie stage IA. The patient was treated with 4 cycles of bortezomib-cyclophosphamide-dexamethasone, plus intensification with melphalan and ASCT. In 02/2016, relapse occurred in the left testis, while the bone marrow was negative. Left orchidectomy was followed by adjuvant radiation therapy (36Gy) and Lenalidomide maintenance. In 01/2018, the patient had no sign of clinical or biological relapse.
Biopsy fixation details: Formalin fixed testis containing a 4.5cm multinodular, poorly defined, whitish tumor.
Frozen tissue available: No.
Details of microscopic findings: The tumor diffusely infiltrated between atrophic seminiferous tubules and was comprised of sheets of atypical, pleomorphic discohesive cells including many large, anaplastic cells with abundant cytoplasm and hyperchromatic, frequently bi- or polylobated nuclei, and numerous medium-sized cells with plasmacytoid features and frequently prominent nucleoli. There were abundant mitoses and apoptotic cells, and small foci of necrosis. The bone marrow contained an interstitial plasma cell infiltrate including few anaplastic cells (**illustration provided**).
Immunophenotype: The tumor cells were CD138+, MUM1+, CD79a+/-, CD20-/+; PAX5- and showed IgA-Lambda restriction, CD45+/-, EMA+/- and MYC+/-, CD56-, cyclin D1-, CD10-, BCL2+, BCL6- and HHV8-. Ki67 index was 85%. EBER in situ hybridization was negative.
Cytogenetics: Performed on CD138-positive sorted cells from the bone marrow aspirate.
FISH: IGH-MAF rearrangement (t(14;16)(q32.2;q23.1))
CGH: gain of 1q21.11q44
Molecular studies: FISH on FFPE sections: no MYC break (Vysis).
Proposed diagnosis: Extramedullary (testicular) plasmacytoma with plasmablastic/anaplastic features.
Interesting feature(s) of submitted case: This challenging case was distinctive by its primary presentation in the testis. Based on the histopathological features, we concluded to a differential diagnosis between an EBV-negative plasmablastic lymphoma with marked plasmacytic differentiation versus an extramedullary plasmacytoma with plasmablastic/anaplastic features. The latter diagnosis was confirmed after bone marrow infiltration was proven.
Extramedullary involvement by plasma cell myeloma (MM) is present in 1-2% cases upon diagnosis (Rajkumar SV. Am J Hematol. 2016;91:719) and the most frequent extramedullary localization is the soft tissues surrounding the skeleton (Varettoni M. Ann Oncol. 2010;21:325). Involvement of the testis by MM is rare (0.6-2.7%) among extramedullary localizations, though it has been suggested that, like for other hematological malignancies, the testis may represent a “sanctuary” for MM (Rosenberg S. J Clin Oncol. 2010;28:e456). Finally, extramedullary relapse without bone marrow involvement by MM is also rare (only 3% of cases; Preety N. Int J Hematol Oncol Stem Cell Res. 2017;11:281). In our case, the patient relapsed in the contralateral testis, and currently remains disease-free under maintenance therapy.

EAHP18-LYWS-323

An unusual cutaneous presentation of extracavitary primary effusion lymphoma

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Case description: A 49-year-old HIV-positive male with a history of IV drug use, an absolute CD4 count of 23 cells/µL, and disseminated Kaposi sarcoma presented with painless, firm 2 cm nodules on the scalp and left jaw. Biopsy of both lesions revealed an extracavitary (e) primary effusion lymphoma (PEL). Following 3 cycles of ICE chemotherapy and 16 weeks of rapamycin while continuing HAART therapy, complete remission of this lymphoma was achieved; the patient continues to remain disease-free eight years later.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: H&E stained sections from both sites show sheets of atypical mononuclear cells dissecting through the deep dermis into the underlying soft tissue, sparing the epidermis and upper dermis. The cells are large with somewhat eccentrically placed round to oval nuclei, vesicular chromatin, prominent eosinophilic, inclusion-like macronucleoli, and abundant pink to amphophilic cytoplasm with occasional paranuclear hofs. Mitotic figures and apoptotic bodies are frequent.
Immunophenotype: The large atypical cells are positive for CD4 (subset dim), CD30 (subset; membrane and Golgi distribution), CD45, HHV8 (LANA), and EBER1. They are negative for CD1a, CD3, CD5, CD8, CD15, CD20, CD21, CD23, CD34, CD43, CD45RO, CD56, CD57, CD68, CD79a, CD117, CD138, CD163, PAX5, Ig-Kappa, Ig-Lambda, Tdt, MPO, ALK, EMA, granzyme B, TIA1, TCRβ, TCRδ, S100, HMB45, OCT3/4, CK7, CK20, CAM5.2, AE1/3, and PLAP.
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Extracavitary primary effusion lymphoma
Interesting feature(s) of submitted case: PEL is an HHV8-associated large B-cell neoplasm, often with co-infection by EBV, that classically presents as a cavitary serous effusion without an associated solid component in the setting of HIV. Within the spectrum of disease is the extremely rare extracavitary subtype, which has the converse presentation of a solid mass without a malignant effusion. Cutaneous involvement is exceptionally rare, particularly cases in which cutaneous lesions are the first manifestation of disease (5 reported cases to date).

PEL is an aggressive disease with poor prognosis and a median survival of 3-6 months. The patient's survival of >8 years following treatment is striking and highly unusual.

The immunoblastic/plasmablastic morphology and deceptively "null" immunophenotype (lack of B and T cell markers) of PEL evokes a broad differential diagnosis that can be diagnostically challenging to resolve.

While ePEL expresses pan-B-cell antigens and CD138 more frequently than PEL with lower expression of CD45, this case showed an opposite immunophenotype more typical of cavitary PEL.

This case demonstrated aberrant, but well-recognized, subset expression of CD4 that may further confound diagnosis.

Although both PEL and ePEL are rare entities, as the lifespan of patients with HIV increases, they may be seen more frequently.

EAHP18-LYWS-137

KSHV/HHV8-Associated Extracavitary Primary Effusion Lymphoma Presenting as Multiple Lymphomatous Polyposis

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Case description: A 49-year-old African-American male was admitted for ongoing vague abdominal pain and 20 pound weight loss within a month. He was found to have severe anemia and required frequent blood transfusion. Review of outside medical record revealed a positive HIV status, which was initially detected in 2015 with very low viral load and no treatment was given since then. An abdominal/pelvic computerized tomography scan was performed which showed focal colonic wall thickening at the splenic flexure, consistent with severe colitis clinically. No significant systemic lymphadenopathy or body cavity effusion was noted by physical examination. No hepatosplenomegaly was identified. Esophagogastroduodenoscopy and colonoscopy were subsequently performed which showed 5 duodenal polyps and innumerable (>100) colonic polyps (too many to count). No discrete nodules or frank masses were identified. Multiple polyp biopsies from duodenum to rectum were submitted for pathologic evaluation.
Biopsy fixation details: Formalin fixed
Frozen tissue available: N/A
Details of microscopic findings: The histologic features of the multiple biopsies were very similar. Review of the biopsy sections from the duodenum to the rectum demonstrated multiple polyploid lesions with relatively preserved intestinal mucosa epithelium but a markedly expanded in the lamina propria with proliferation of large mononuclear cells. No obvious lymphoepithelial lesions were seen. Focal surface erosion was identified. The infiltrating mononuclear cells were medium to large in size, having moderate amount of amphophlic cytoplasm, round to irregular nuclear contours, vesicular chromatin and prominent nuclei. Some morphologic features imparted a plasmablastic appearance (Figure 2). Increased in mitotic figures and apoptotic bodies were frequently seen.
Immunophenotype: Immunohistochemical studies demonstrated that the infiltrating cells were completely negative for cytokeratin, S-100 protein, myeloperoxidase, OCT3/4, CD3, CD20, CD79a, PAX-5, CD56 CD138, kappa or lambda light chains, essentially making common un-differentiated carcinoma, melanoma, germ cell tumor, common types of lymphoma, myeloma and myeloid sarcoma unlikely. However, they strongly expressed CD30, MUM-1, c-MYC protein, Bob-1 and the tumor cell nuclei were strongly positive for LANA of HHV8/KSHV (Figure 3). A subset of tumor cells was also positive for Oct-2 and CD38. EBV in situ hybridization and EBV-LMP by immunohistochemistry were negative. Ki67 highlighted approximately 95% of nuclei.
Cytogenetics: N/A
Molecular studies: Immunoglobulin heavy and kappa light chain gene rearrangements were detected by PCR analysis. No evidence of c-Myc gene rearrangement was detected by interphase FISH analysis
Proposed diagnosis: KSHV/HHV8-Associated Extracavitary Primary Effusion Lymphoma Presenting as Multiple Lymphomatous Polyposis
Interesting feature(s) of submitted case: Extracavitary PEL presenting as distinctive multiple lymphomatous polyposis as the current case has not been described previously and may represent a novel clinical presentation and behavior of this rare disorder.

EAHP18-LYWS-386

Hairy cell leukemia presenting as a dural-based mass mimicking meningioma

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Case description:
A 45-year-old man presented with headaches. Brain MRI with contrast showed a dural-based avidly enhancing mass in the right temporo-occipital lobe, up to 6.0 cm in AP dimension, with a dural tail, consistent with meningioma; the brain was otherwise normal. In retrospect, prior imaging done 4 years earlier during a syncopal episode showed a smaller lesion at the same site. The patient underwent surgical resection of the dural-based tumor (submitted case).

CBC showed a very mild leukopenia and thrombocytopenia with blood smear showing rare (2%) atypical lymphocytes. A staging bone marrow biopsy was normocellular with mild reticulin fibrosis and extensive involvement by hairy cell leukemia. Flow cytometry confirmed the diagnosis, with tumor cells expressing CD19, CD20, CD25, CD11c, CD103, and kappa light chain restriction.

On further history, the patient reported that there were at least four family members on his paternal side with a known diagnosis of hairy cell leukemia (including great aunt, great grandfather and his two daughters), as well as a great uncle with myelodysplastic syndrome.

The patient received a single course of cladribine (2-CDA) and has remained in remission.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings:
Sections of the dural mass demonstrated fibrovascular tissue with an extensive sheet-like infiltrate of highly monomorphic small cells with ovoid to indented nuclei, smooth nuclear contours, inconspicuous nucleoli, and abundant amphophilic cytoplasm (“fried egg” appearance). Thin-caliber branching vessels were distributed throughout the proliferation.
Immunophenotype:
The abnormal cells expressed CD45, CD20, PAX5, CD43, CD11c, CD25, CD123, TRAP, cyclin D1, IgD, IgM (focal), and BCL6. Reticulin stain showed a diffuse increase in reticulin fibers. Abnormal cells were negative for CD5, CD10, CD23, CD138, kappa, lambda, SOX11, keratin, S100, and EMA. Ki67 proliferation index was less than 5%.
Cytogenetics: FISH was negative for CCND1/IGH translocation.
Molecular studies: BRAF-V600E mutation was detected by PCR
Proposed diagnosis: Hairy cell leukemia
Interesting feature(s) of submitted case:
Extramedullary/ extrasplenic presentations of hairy cell leukemia are very rare, and, when present, occur mostly in the liver, lymph nodes (particularly abdominal), and skin. Other anatomic sites are exceptional, described in isolated case reports, including rare CNS and meningeal involvement. This patient’s presentation as a dural mass, clinically and radiologically compatible with meningioma, was diagnostically challenging. Lymphoid neoplasms of the dura are unusual and mostly represent MALT lymphomas; a wide index of suspicion is therefore necessary to diagnose hairy cell leukemia at atypical sites. Finally, the patient’s strong family history of hairy cell leukemia is notable. Hairy cell leukemia has been previously reported in at least 15 families, some with particular associated HLA haplotypes, although the reported familial cases do not appear to have a higher propensity for extramedullary disease.
References: Chaudhry MS et al. Am J Hematol 2011;86:423-4; Tadmor T, Polliack A.Best Pract Res Clin Haematol 2015(4):193-9; Villemagne et al. Leuk Lymph 2005;46(2):243-45

EAHP18-LYWS-148

T-PLL infiltrating the heart

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Case description: A 68-year-old man presented with rapidly progressive dyspnea due to newly diagnosed heart failure. Cardiac magnetic resonance imaging was compatible with myocarditis. Coronary angiography showed no relevant stenosis. The endomyocardial biopsy showed a multifocal, partially active lymphocytic myocarditis. PCR for several viruses were negative. The patient was treated with beta-blockers, angiotensin-receptor blockers, diuretics, amiodarone and a statin.
Four years later, a bone marrow biopsy was performed due to lymphocytosis and thrombopenia, and demonstrated a CD2, CD3, CD5, CD7, CD26 and CD4/CD8 double-positive T lymphocytosis with a biclonal T-cell receptor rearrangement. Cytogenetics revealed a complex karyotype including an inversion of chromosome 14 and isodicentric chromosome 8. The diagnosis of T-prolymphocytic leukemia (T-PLL) was established. The patient received a left ventricular assist device due to progressive heart failure. The apical myocardial biopsy showed destructive lymphocytic infiltration by the T-PLL which was proven to be of the same clonal T-cell origin as in the bone marrow. Reanalysis of the myocardial biopsy taken 4 years earlier revealed a clonal T-cell population matching with 1 of the current T-cell gene rearrangement products. The patient was treated with alemtuzumab, followed by a cytokine storm. He refused further treatment and died soon after. This case illustrates a destructive cardiac infiltration by T-PLL causing severe heart failure.
Biopsy fixation details: Myocardial biopsy (2014), formalin-fixed paraffin embedded (FFPE)
Biopsy of 2010 not available (outside hospital)
Frozen tissue available: none
Details of microscopic findings: The apical myocardial biopsy demonstrates multifocal, destructive infiltration by small to medium-sized lymphocytes with round, slightly irregular nuclear contours.
Theadjacent cardiomyocytes show reactive/regenerative changes.
Immunophenotype: PB/BM: CD2, CD3, CD5, CD7, CD26 and CD4/CD8 double-positive
Heart: CD2, CD3, CD5, CD7 and CD4/CD8 double-positive (TCL1 not evaluable)
Cytogenetics: BM: complex karyotype including an inversion of chromosome 14 and isodicentric chromosome 8
Molecular studies: none
Proposed diagnosis: T-prolymphocytic leukemia (T-PLL) infiltrating the heart
Interesting feature(s) of submitted case: This case illustrates a destructive cardiac infiltration by T-PLL causing severe heart failure.
(published as “Broken heart by T-prolymphocytic leukemia” C. Arranto and A. Tzankov
”Images in hematology” BLOOD, 3 AUGUST 2017 VOLUME 130, NUMBER 5)

EAHP18-LYWS-316

Gastric involvement by adult T-cell leukemia/lymphoma in a patient from a non-endemic HTLV1 area

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Case description: A 61-year-old man, born and raised in Philadelphia, presented with generalized weakness and abdominal pain. A maternal grandmother of potential Caribbean descent was identified, though the patient had reportedly little to no direct contact with her. Laboratory studies showed a leukocytosis of 29 x 10^9/L that rapidly rose to 225 x 10^9/L, as well as hypercalcemia (11.4 mg/dL). An endoscopy performed for the abdominal pain revealed diffuse moderate inflammation of the stomach, and biopsies of the antrum and body, as well as antral ulcers and a fundic gland polyp, were performed. A right inguinal lymph node was also biopsied. HTLV1/2 was positive by serology and western blot. Despite therapy, the patient became critically ill in the setting of overwhelming tumor burden and died one month after initial presentation.
Biopsy fixation details: Formalin **Frozen tissue available:** No
Details of microscopic findings: H&E stained sections show gastric oxyntic and antral mucosa with infiltration of the lamina propria and submucosa by atypical medium to large, discohesive cells with irregular nuclear contours. Occasional atypical mitoses are identified. This infiltrate is evident in all gastric biopsy sites except the ulcerations.
On peripheral blood smear, numerous medium to large atypical lymphocytes with convoluted and occasionally polylobated nuclei (“flower cells”) are noted.
Immunophenotype: Gastric biopsies: IHC--CD2+, CD3+, CD4+, CD5+, CD30+ T-cells. Ki-67 (~70-80%). CD7-, CD8-, CD20-
Lymph node: IHC--Identical phenotype. Additionally, FOXP3 and CD25 focally positive. Flow--CD3(dim)+ CD5(dim)+ CD4+ CD25+ CD7- CD8- T-cells
Cytogenetics: Not performed
Molecular studies: Monoclonal T cell-receptor gamma gene rearrangement present.
Proposed diagnosis: Adult T cell leukemia/lymphoma (ATLL).
Interesting feature(s) of submitted case: 1. ATLL in a non-endemic area: The patient was HTLV1 positive despite never having travelled beyond the Philadelphia area. It is possible he contracted the HTLV1 virus from two generations of vertical transmission via breastfeeding (the most common route of transmission). Recent studies have shown a significant increase in the incidence of ATLL in non-endemic areas while that in endemic areas has not increased. It is predicted that there will be a doubling of incidence in the USA in the next decade. This trend may reflect the migration of HTLV1 carriers from endemic areas, suggesting that additional attention should be paid to prevention in non-endemic areas.
2. Gastric involvement by ATLL: While skin is recognized as the most common extra-lymphoid site of involvement, gastrointestinal (GI) tract is a well-known but perhaps underappreciated site of involvement. An autopsy study in 1993 showed GI tract involvement in 70% of patients with the stomach being most frequent site of involvement in the GI tract (40%). More recently, a potential relationship between ATLL gastric involvement and H. pylori infection was described, with H. pylori infection found in 86% of patients with gastric involvement, and only 38% of patients without gastric involvement. This may be mediated by enhanced expression of homing adhesion molecules (LFA-1) on ATLL cells and of their ligands (ICAM-1) on endothelial cells, which is markedly enhanced in H. pylori infected mucosa. In our case, H. pylori stains were negative.

EAHP18-LYWS-149

Pediatric-type follicular lymphoma presenting in gastrointestinal tract

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Case description: 13 yeard old male presented with a 1 month history of intermittent episodes of epigastric pain. CT showed an ileocolic intussusception, and the patient underwent surgical excision of a portion of the small bowel (ileum) which inculded an area resembling a large Peyer's patch.
Biopsy fixation details: 10% buffered formalin.
Frozen tissue available: No
Details of microscopic findings: The florid lymphoid infiltrate appears to consist of a single enlarged follicle, composed almost entirely of intermediate size cells with centroblastic morphology.
Immunophenotype: The cells are positive for CD20, CD10, and show weak coexpression of MUM1 and CD43. Kappa light chain restriction is present. Ki67 proliferative staining is high.
Cytogenetics: Negative for MUM1/IRF4, BCL2, BCL6 or MYC rearrangements by FISH.
Molecular studies: Positive for immunoglobulin heavy chain gene rearrangement.
Proposed diagnosis: Pediatric-type follicular lymphoma presenting in the gastrointestinal tract.
Interesting feature(s) of submitted case: Unusual localization for this entity. Differential diagnosis includes a florid follicular hyperplasia with clonality, and systemic follicular lymphoma. The patient has no lymphadenopathy or systemic symptoms.

EAHP18-LYWS-151

T-cell prolymphocytic leukemia presenting with liver involvement and relapsing as peritonitis due to tumor infiltration of the small bowel and colon.

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Case description: The patient is a 68 year old previously healthy woman who presented with jaundice. The total bilirubin was 10.7 mg/dL (ref, 0.3-1.2) and alkaline phosphatase was 361 mg/dL (ref, 32-91). At the same time patient's WBC was found to be markedly elevated at 165 x 10^3/uL. Liver biopsy and bone marrow biopsies were diagnostic of T-cell prolymphocytic leukemia. Patient has been treated with Campath and achieved complete hematologic remission. Eight months following the initial presentation, patient was hospitalized due to clinical and laboratory evidence of peritonitis. Exploratory laparotomy showed evidence of right colon ischemia and tumor infiltration along colon, appendix and small bowel mesentery. Patient's condition continued to deteriorate and she expired nine months after the initial diagnosis.
Biopsy fixation details: Formalin
Frozen tissue available: No
Details of microscopic findings: Liver biopsy: morphologic evaluation of the liver biopsy shows significant infiltration of the sinuses as well as expansion of the portal areas by a small lymphoid cell population. These cells appear to have round to irregular nuclear contours and a scant amount of cytoplasm.
Terminal Ileum, cecum, appendix, right colon, and transverse colon: the intestinal wall is markedly thickened and edematous with evidence of chronic inflammation. The lymphocytes are small with round nuclei and scant cytoplasm. The lymphoid infiltrate focally involves the muscularis propria and the subserosal surface and extends into the peritoneal adipose tissue. Right colon has focal areas of acute inflammation, edema and necrosis, consistent with early ischemic colitis.
Immunophenotype: The atypical lymphoid cells are composed predominantly of CD3+ T-lymphocytes with rare CD20+, Pax-5+ B-cells. T cells coexpress CD4 (weak, partial) and CD8 (bright). Tumor cells are positive for CD2 and CD5 and have partial loss of CD7. TCL-1 is positive. Neoplastic cells are negative for ALK1, CD30, TdT, TIA1 and granzyme B. In situ hybridization is negative for EBV (EBER1). Ki67 nproliferative fraction is low at <5% of all cells.
Cytogenetics: A normal female karyotype is observed. FISH analysis identified gain of 8q in 58% of the cells evaluated. TCL1 gene is rearranged in 51% of 200 interphase nuclei evaluated by FISH analysis.
Molecular studies: A monoclonal T cell population is identified by PCR.
Proposed diagnosis: T-cell prolymphocytic leukemia.
Interesting feature(s) of submitted case: The patient presented with symptoms related to liver involvement. After achieving good response with alemtuzumab, she relapsed due to diffuse infiltration of gastrointestinal tract, resulting in right colon ischemia. At the time of the relapse, the CBC was normal with no evidence of lymphocytosis.

EAHP18-LYWS-154

Primary cutaneous small lymphocytic lymphoma/chronic lymphocytic leukemia of the penis with inguinal nodal HSV necrotizing lymphadenitis mimicking Richter transformation

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Case description: A 74-year-old male presented with a penile ulcer and subsequent groin swelling. He had sustained injury to his penis during sexual intercourse approximately 10 days previously. He was treated with IV antibiotics. A CBC showed: WBC 5.4 x 10^9/L with 48% lymphocytes. A biopsy of the skin lesion and excisional biopsy of the enlarged left inguinal lymph node was performed.
Biopsy fixation details: Formalin fixed and paraffin embedded.
Frozen tissue available: No
Details of microscopic findings: Penile skin lesion H&E stained sections reveal a dense, deep, non-epidermotropic infiltrate of cytologically monotonous small lymphocytes with round nuclei and condensed chromatin, and infrequent scattered large cells, underlying a focally ulcerated epidermis.
Left inguinal lymph node H&E stained sections reveal abundant areas of suppurative and granulomatous necrosis. In viable regions, there is a monotonous small lymphocytic expansion, similar to that noted in the penis. Paler areas reflecting pseudofollicular proliferation centers are evident. In many areas, there is an additional expansion of larger cells with dispersed chromatin and prominent nucleoli that are mostly singly distributed rather than forming expansive sheets. These areas are associated with frequent tingible-body macrophages, apoptotic debris, and mitoses, generating a "starry-sky" appearance under low power. Large cells in or adjacent to the necrotic areas show chromatin clearing with occasional eosinophilic material that resembles Cowdry type A inclusions.
Immunophenotype: Penile skin lesion By IHC, the majority of the cells present within the dermis and subcutis are CD20+, CD5+, CD23+, CD10- B-cells with fewer CD3+ T-cells. HSV1/2 is negative.
Left inguinal lymph node Flow cytometry reveals an expansion (78%) of monoclonal (dim SmIg-kappa) CD19+ CD20+ B-cells that coexpress CD5, CD23 and CD38. By IHC, the neoplastic cells express CD20, CD79a, PAX5, CD5, CD21, CD23, and BCL2. Ki67 is positive in ~10% of cells in the small cell areas and ~50% in the larger cell areas. They are negative for CD10, CCND1, SOX11, MUM1 and MYC. The large cells associated with necrosis are HSV1/2+, but negative for VCV and EBER1.
Cytogenetics: FISH studies on the lymph node are borderline positive for trisomy 12 and negative for deletion/monosomy 13, ATM deletion, TP53 deletion, MYC translocation and t(11;14).
Molecular studies: None
Proposed diagnosis: Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) of both the penile skin and left inguinal lymph node, with herpes simplex necrotizing lymphadenitis in the lymph node mimicking Richter transformation.
Interesting feature(s) of submitted case: SLL/CLL presenting as a primary cutaneous lesion is extremely rare. Subsequent inguinal swelling revealed nodal involvement that appeared to be more proliferative with foci of increased larger cells. The large cell areas are interpreted to reflect the associated herpes simplex viral infection, rather than transformation of the underlying SLL/CLL. This viral infection likely reflects reactivation in the setting of immunosuppression that accompanies SLL/CLL and the activation of the neoplastic small cells may mimic large cell transformation. There was no evidence of an absolute lymphocytosis in the concurrent CBC.

EAHP18-LYWS-168

Small bowel Anaplastic Large Cell Lymphoma ALK positive

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Case description: 25 year old male previously well presented with small bowel intussusception. On laparotomy, there was a small bowel mass with mesenteric lymphadenopathy. Patient also has a pulmonary mass.
Biopsy fixation details: 10% buffered formalin fixed and paraffin embedded.
Frozen tissue available: No
Details of microscopic findings: Sections of the small bowel show a tumour composed of large lymphoid cells. The tumour is present in the submucosa. The lymphoid cells display moderate to marked nuclear pleomorphism and the cells contain eosinophilic cytoplasm. The tumour cells display prominent nucleloli. Some of the tumour cell nuclei are kidney shaped and eccentrically placed (hallmark cells) and occasional wreath like cells are also present. Extensive tumour necrosis is seen and tumour mitoses are readily identified. The overlying mucosa is unremarkable with no villous atrophy or difinitive intraepithelial lymphocytosis.
Immunophenotype: Positive: CD45, CD45RO, CD4, CD30, ALK-1, EMA, CD25, perforin, granzyme B, bcl-6, c-myc.
Negative: CD20, PAX5, CD2, CD3, CD5, CD7, CD8, CD79a, CD56, TIA-1, TCR BF-1, TCR delta, CD10, PD-1, EBER ISH.

Cytogenetics: Not done
Molecular studies: Not performed
Proposed diagnosis: Anaplastic large cell lymphoma ALK positive
Interesting feature(s) of submitted case: Involves the small bowel as the primary mass leading to intussusception and presence of pulmonary mass.

EAHP18-LYWS-169

Primary testicular extranodal NK/T-cell lymphoma, nasal type with STAT3 mutation in non-EBV-endemic area

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Case description: A 73-year-old man with previous history of prostatic adenocarcinoma (stage pT2b pN0 cM0 Gleason score 8), status post radical prostatectomy in 2000 with local recurrence in perivesicular soft tissue and bone metastasis in 2016, presented in 2017 with a right testicular mass. Right orchiectomy was performed. Bone marrow biopsy was negative and the patient was considered in Stage IAE. He is planned to receive radiochemotherapy.
Biopsy fixation details: 4% buffered formalin
Frozen tissue available: no
Details of microscopic findings: The testis showed geographic necrosis with apoptosis, hemorrhage and viable lymphoid cells in diffuse pattern with angiocentricity and angiodestruction. Cytologically, the lymphoid cells varied from medium-sized to large with irregularly folded nuclei, granular chromatin, generally inconspicuous nucleoli, eosinophilic cytoplasm, frequent mitoses and apoptosis.
Immunophenotype: The tumor cells were positive for CD3, CD56, TIA1, granzyme B and phospho-STAT3, but negative for CD20, CD4, CD5, CD7, CD8 and BF1. CD30 stained scattered large cells. The proliferation index of the tumor was up to 60% by Mib1. P53 stain was strongly positive in scattered large cells. EBER was positive in most tumor cells.
Cytogenetics: no
Molecular studies: A custom AmpliSeq panel designed for sequencing the most frequent mutated genes of extranodal NK/T-cell lymphoma (STAT3, STAT5B, JAK3, DDX3X, TP53, MGA, MSN and BCOR) was applied using Ion Torrent PGM Sequencer. The mean coverage was 9030 reads. A somatic mutation of STAT3, encoding an amino acid substitution at p.D566N with a 20% variant allele frequency was identified.
Proposed diagnosis: Primary testicular extranodal NK/T-cell lymphoma, nasal type with STAT3 mutation
Interesting feature(s) of submitted case: 1) This case has typical morphology and immunophenotype of extranodal NK/T-cell lymphoma (ENKTL), but this rarely happens in Western population and unusually in extranasal site. ENKTL is more prevalent in Asians and the indigenous populations of Mexico, Central and South America.
2) Primary testicular lymphoma (PTL) is an uncommon, heterogeneous group of extranodal lymphoma, accounting for 1% to 2% of extranodal NHL. The majority of cases are diffuse large B-cell lymphoma (DLBCL). Exceptional cases of primary MALT lymphoma, mantle cell lymphoma, follicular lymphoma, Burkitt lymphoma, ENKTL, PTCL, NOS and ALK-negative ALCL have been reported. The predilection sites of testicular ENKTL are skin, CNS, GI tract and lung. Lymphomas arising under the selective pressure of immune surveillance may develop an immune escape phenotype. This patient has a prostatic carcinoma that could induce, to some extent, immunodeficiency or dysregulation, favoring the development of the testicular ENKTL.
3) To date, there are seven large-scaled studies on the mutational landscape of ENKTL. STAT3 mutation has been reported in 26 out of 261 (10%) of cases ranging from 0% to 26.5%. Our case has a point mutation in STAT3, encoding an amino acid substitution at p.D566N. This position is in DNA-binding domain near the SRC homology (SH2) domain, which is the most frequent domain of mutation of STAT3 gene. STAT3 inhibitor could be a therapeutic target in a subset of ENKTL with activating STAT3 mutation and this was proved in cell line by Sim et al.

EAHP18-LYWS-170

Extranodal NK/T-cell lymphoma, nasal type, with low grade features

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Case description: A 71-year-old woman presented to an outside hospital with chronic rhinosinusitis and postnasal drip with new onset of sinus symptoms (congestion, cough and fever). Her symptoms did not resolve with antihistamines, two courses of prednisone and 6 weeks of antibiotics. The patient has h/o seasonal allergies, generally occurring in June due to tree pollen allergy and resolving with antihistamines +/- antibiotics. She was referred to an ENT physician for a biopsy of the intranasal lesion. CT scans of chest, abdomen, and pelvis were only remarkable for scattered pulmonary infiltrates and sinonasal thickening. Biopsy of the intranasal lesion was performed at the outside institution and diagnosis of NK/T-cell lymphoma, nasal type was rendered. Re-review at our institution was consistent with this diagnosis however only selected slides were available for the review and the tissue was extremely scant. PET/CT performed 2 months after the initial presentation revealed FDG-avid soft tissue thickening in the nasopharyngeal cavity in keeping with the lymphomatous involvement. The patient remained largely asymptomatic except for some postnasal drip. A re-biopsy was performed at our institution 3 months after the initial diagnosis for re-evaluation of the nasal lesion.
Biopsy fixation details: The biopsy specimen was fixed in formalin.
Frozen tissue available: No
Details of microscopic findings: H&E-stained slides show sinonasal mucosa with an atypical lymphoid infiltrate in the lamina propria. The infiltrate consists predominantly of small lymphoid cells with irregular and hyperchromatic nuclei with scant to moderate cytoplasm. Scattered neutrophils and eosinophils are also noted.
Immunophenotype: Immunohistochemical stains performed with adequate controls showed that the majority of the atypical lymphoid cells stain positive for CD2, CD3, CD5, Granzyme B (subset), and perforin (subset). These abnormal T cells lack expression of CD7, and also stain negative for CD56, CD57, CD30, TCR-gamma and TCR-delta. TCR-beta stains a small subset of cells. In situ hybridization for latent Epstein Barr virus RNA is positive. CD4 and CD8 stain occasional scattered cells, with a CD4:CD8 ratio of ~4:1. TIA-1 stains the CD8+ T cells, but is negative in the atypical T cells. The Ki-67 proliferative index is ~1%.
Flow cytometric studies performed on the right nasal biopsy demonstrated a population of immunophenotypically aberrant CD2+ surface CD3- CD5(dim)+ CD7(dim)+ CD16- CD25- CD56- NK cells (6% of total events).

Cytogenetics: Not performed
Molecular studies: T-cell receptor gamma gene rearrangement studies by PCR were positive and revealed a 239 bp peak in the V-gamma Reaction 1 and 192 bp and 193 bp peaks V-gamma Reaction 2 in an irregular polyclonal distribution.
DNA sequencing studies revealed a missense variant in exon 3 of KIT at amino acid 167 converting the wild type residue, Lysine, to Methionine (KIT p.K167M c.500A>T) with an allele frequency of 23%.

Proposed diagnosis: Extranodal NK/T-cell lymphoma, nasal type, with low grade features

Interesting feature(s) of submitted case: This NK/T-cell lymphoma is unusual as it shows very low proliferative index and an indolent clinical course. This lymphoma is also CD56 negative whereas the majority of the extranodal NK/T-cell lymphomas are positive. In addition, a variant of uncertain significance was detected in KIT gene.

EAHP18-LYWS-197

Extranodal NK/T-cell lymphoma, nasal type, presenting in the testicle

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Case description: A 70 year-old Caucasian male, presented with a painless, right testicular mass. Blood AFP/hCG tests were negative. A right orchiectomy revealed an aggressive extranodal NK/T-cell lymphoma, nasal type. No other mass lesion or lymphadenopathy was detected by PET-CT scan, and staging BM examination was negative. A year later, after chemotherapy, the lymphoma relapsed, with extensive involvement of the right oropharynx, right orbital space, PB and BM. His hospital course was complicated by infection, GI bleeding and DIC, and he died a year after initial diagnosis
Biopsy fixation details: Testicular, tonsillar and submandibular tissue samples fixed in formalin, BM core biopsy fixed in Bouin's solution. Fresh tissue submitted for flow cytometry and cytogenetic and molecular analysis.
Frozen tissue available: Yes, from the testicular, right tonsillar and right submandibular masses.
Details of microscopic findings: The testicular mass showed a dense and diffuse lymphoid infiltrate effacing the testicular parenchyma. The lymphocytes were medium to large in size, had irregular nuclei, clumped chromatin, small nucleoli and scant cytoplasm. Mitotic figures and apoptotic bodies were frequent and foci of angio-centricity and angio-invasion were present. The right tonsillar mass and second BM biopsy (at relapse) showed extensive lymphocytic infiltrates with similar cytomorphologic features.
Immunophenotype: By IHC, the lymphocytes expressed CD2, CD3 (cytoplasmic?), CD56, TIA-1, Perforin, BCL2 (weak, subset). EBERish was positive. ALK-1, MUM1, BCL6 and P53 were negative. Ki-67 showed a high proliferative index (90%). C-MYC showed variable staining in 30-40% of the lymphocytes. Aberrant p53 expression was seen in 90% of cells in the tonsillar relapse. Flow cytometry of the testicular and tonsillar masses, and BM and PB samples highlighted atypical NK-cells that had the following phenotype: CD56+, CD2+, CD38+, CD43+, HLA-DR+, CD3-, CD5-, CD7-, CD4-, CD8-, CD16-, CD57-, CD25-, TCR alpha/beta-, TCR gamma/delta-, PD-1- and CD103-.
Cytogenetics: G-band karyotype of the right testicular mass:
49,XY,+7,+der(7)t(1;7)(q21;p15),+8,del(8)(q12q22)x2,-19,+mar[16]/46,XY[3]
G-band karyotype of the right tonsillar mass: 45,X,-Y,der(8)t(8;19)(p11.2;p12)del(8)(q12q22),der(16)t(9;16)(q12;p13.3)[15]
G-band karyotype of the bone marrow aspirate:
46,XY,der(8)t(8;19)(p11.2;p12)del(8)(q12q22),der(16)t(9;16)(q12;p13.3)[5]/45,idem,-Y[2]/46,XY[13]
Molecular studies: TCR-Beta gene rearrangement analysis by PCR showed polyclonal products.
Proposed diagnosis: Extranodal NK/T-cell lymphoma, nasal type.
Interesting feature(s) of submitted case: This lymphoma presented primarily as a testicular mass, consistent with a primary testicular extranodal NK/T-cell lymphoma, nasal type. Only rare cases of extranodal NK/T-cell lymphoma, nasal type with initial testicular presentation are documented in the English literature. In addition, this disease typically presents at a younger age in Asian patients, while the current case occurred in an older Caucasian individual. Interestingly, the lymphoma upon relapse, involved the tonsillar and submandibular regions, as well as the orbit, bone marrow and peripheral blood, while the common sites at relapse reported in the literature (in decreasing frequency), are the contralateral testis, followed by lymph node, spleen, liver, skin, nasopharynx and bone marrow. Cytogenetic analysis showed a complex karyotype at diagnosis, with differences noted in the relapsed tonsillar and bone marrow samples, suggestive of cytogenetic evolution/progression.

EAHP18-LYWS-218

NK/T-cell lymphoma nasal-type of the testis

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Case description: A 56-year-old man presented with enlarged left testis that was removed in the suspect of a seminoma. Eighteen months after surgical resection the disease recurred with a mass at the homolateral kidney hylum. BEAM chemotherapy was performed but disase recurred again with meningeal involvement, hepato-splenomegaly and lymph adenopathy that followed. After chemotherapy, radio-therapy and autologous hematopoietic stem cell transplantation, the patient died of disease 55 months after first diagnosis**.**
Biopsy fixation details: Formalin fixed, paraffin embedded.
Frozen tissue available: None
Details of microscopic findings: Medium to large atypical cells, with high mitotic rate, diffusely infiltrated the testicular parenchyma, surrounding and infiltrating the tubules, and extending outside the tunica albuginea. Neoplastic cells occupied the lumen of some vessels; focal necrosis was evident.
Immunophenotype: Atypical cells expressed CD2, CD3, ZAP70, CD56, TIA1 and perforin and were positive for EBV infection (EBER 1/2). No reactivity was found for CD2AP, CD4, CD5, CD8, CD20, CD30, CD34, CD68, CD79a, CD123, CD117, CD138, Ig light chans, TdT, myeloperoxidase, cytokeratins and PLAP.
Cytogenetics: Not performed
Molecular studies: T-cell receptor showed clonal rearrangement.
Proposed diagnosis: Extranodal NK/ T-cell lymphoma, nasal type
Interesting feature(s) of submitted case: Primary testicular NK-T cell lymphoma of nasal-type is unusual and its diagnosis may be challenging. This case shows a prototypical phenotype with unusual TCR clonal rearrangement suggesting cytotoxic T-cell derivation.

EAHP18-LYWS-222

ALK-positive large B-cell lymphoma presenting as a gastric ulcer.

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Case description: 63 year old male presenting with poor appetite, lethargy and weight loss for 6 months. More recently developed night sweats. At upper GI endoscopy, there was a 2cm diameter, chronic ulcer in the posterior cardia which was biopsied. A right level IV neck node was subsequently biopsied. (Submitted slides are from nodal mass as insufficient tissue remains from gastric biopsies). CT showed cervical, mediastinal, mesenteric and retroperitoneal lymphadenopathy, as well as thickening of the wall of the stomach, bladder and rectum.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Gastric mucosa infiltrated by a diffuse population of malignant cells filling the lamina propria. The cells are large with a vaguely plasmablastic morphology with abundant, eccentrically placed eosinophilic cytoplasm. There is a high rate of proliferation and apoptosis.
Immunophenotype: Positive: ALK-1 (granular cytoplasmic staining), MUM-1, bcl-2, bcl-6 (weak and focal), CD138, CD56 (weak and focal), lambda light chain, EMA (focal), vimentin, cytokeratin AE1/3 (focal), PAN CK (focal)
Negative: CD3, CD4, CD5, CD10, CD20, CD45, CD57, CD79a, PAX5, kappa light chain, perforin, granzyme B, TIA-1, HHV8, EBV (EBERs), cytokeratins 5/6, 7, 14, 19, 20, CDX2, TTF-1, melan A, S100, chronogranin A, synaptophysin, p63, BerEP4, desmin, SMA, calponin, caledesmon
Equivocal: IgA, IgG, IgM, CD30
Ki67 staining in about 100% of cells.
Cytogenetics: Not done
Molecular studies: Not done
Proposed diagnosis: ALK-positive large B cell lymphoma
Interesting feature(s) of submitted case: This was a gastrointestinal presentation of a rare tumour. The lack of expression of CD45 and lymphoid lineage markers CD3 and CD20 (and focal positivity for cytokeratin cocktails and EMA) proved a diagnostic pitfall with lymphoma initially not considered in the differential diagnosis on this basis.

EAHP18-LYWS-226

Intravascular large B-cell lymphoma presenting in the lung and associated with hemophagocytic lymphohistiocytosis

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Case description: A 65-year-old Caucasian woman with a remote history of lyme disease, babesiosis and hypothyroidism, presented with recurrent fever, headache, constitutional symptoms, dry cough, and bilateral non-pruritic palmar rashes. Lab tests were significant for anemia (Hb 8.4g/dL), markedly elevated inflammatory markers (ESR-117mm/hr, CRP-176 mg/L, Ferritin-846ng/mL) and mildly elevated liver enzymes (AST-78U/L, ALT-78U/L). An extensive infectious and rheumatology workup was negative. Imaging studies including a PET scan were unrevealing. The patient's symptoms improved with empiric steroid therapy. Three months later, the patient developed shortness of breath, and was found to be hypoxic. CBC showed worsening anemia and thrombocytopenia. Ferritin (1125 ng/mL) and Interleukin-2 receptor levels (12430pg/mL) were markedly elevated and hypertriglyceridemia was noted, findings consistent with hemophagocytic lymphohistiocytosis (HLH). A lung wedge biopsy was performed, which unexpectedly revealed intravascular large B-cell lymphoma. The bone marrow was also involved. The patient's clinical course was complicated by multiple infections while on chemotherapy and she died of respiratory failure one year after initial presentation.
Biopsy fixation details: Lung tissue samples were fixed in formalin, bone marrow core biopsy was fixed in Bouin's solution. Fresh tissue was submitted for flow cytometry and cytogenetic and molecular analysis.
Frozen tissue available: No
Details of microscopic findings: The lung wedge biopsy showed atypical, medium to large-sized lymphocytes that had ovoid to irregular nuclei and variably prominent nucleoli, confined to the pulmonary blood vessel lumens. The lung parenchyma was spared. The bone marrow biopsy showed intravascular and interstitial infiltrates of medium to large-sized lymphocytes with similar cytomorphology.
Immunophenotype: By IHC, the cells were positive for CD20, PAX5, CD5, BCL2, BCL6, MUM1 and C-MYC (40% of cells), and negative for CD10, CyclinD1 and EBV (by EBERish). The Ki-67 proliferation index was >90%.
Flow cytometry analysis of the bone marrow aspirate sample highlighted an aberrant kappa light chain-restricted B-cell population with the following immunophenotype: CD19+, CD79a+, CD20+, CD5+, CD10-, CD11c-, CD23-, CD25+, CD43+, CD103-, s/c IgM+, IgD-, and HLA-DR+.
Cytogenetics: G-band karyotype of the bone marrow aspirate:
47,XX,del(2)(q31q33.2),der(7)t(3;7)(q22;q32),+18,der(19)t(11;19)(q13;p12),add(21)(p11.2)[7]/46,XX[18]
FISH analysis showed no rearrangement of BCL2, BCL6 or IGH, but detected 3 copies of BCL2 and 3 copies of BCL6 in 16.8% and 15% of cells analyzed, respectively.
Molecular studies: PCR analysis for IGH rearrangement showed a clonal product.
Proposed diagnosis: Intravascular large B-cell lymphoma (IVLBCL) with HLH
Interesting feature(s) of submitted case: Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma characterized by localization of neoplastic lymphocytes to the blood vessel lumens of different organs or body sites. Two variants have been described, the hemophagocytic Asian variant and the classical Western variant. Central nervous system and skin involvement is more commonly seen in the Western variant, while the Asian variant more frequently shows predilection for the liver, spleen and bone marrow and is associated with HLH. Our case is unusual in that the patient was Caucasian with IVLBCL presenting in the lung and had bone marrow involvement and clinical manifestations of HLH. CD5 expression is another unusual feature in this case, which may be associated with an adverse clinical outcome.

EAHP18-LYWS-264

66F- Intracranial- extraaxial lesion

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Case description: A 66 year old female with no previous medical history presented left-hemiparesis. MRI showed an intracranial/ extra-axial enhancing lesion involving the meninges in the right fronto-temporal parietal area. The clinical diagnosis was one of meningiioma. A craniotomy was performed.
Biopsy fixation details: The biopsy specimen was fixed in formalin prior to embedding in paraffin.
Frozen tissue available: Saved frozen tissue is not avaiable.
Details of microscopic findings: The duramater is heavily infiltrated by a diffuse small mature appearing lymphocytes admixed with plasma cells.
Immunophenotype: CD20 positive in small neoplastic lymphocytes.
CD138 positive in plasma cells with kappa light chain restriction.
CD3 positive only in scattered reactive T-cells.
CD10 and CD5 were negative
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Low grade B-cell lymphoma most consisitent with Lymphoplasmocytic lymphoma
Interesting feature(s) of submitted case: Rare site and unusual case of CNS lymphoma.
The differential diagnosis with extranodal marginal zone lymphoma

EAHP18-LYWS-295

Skin and Vagina tumors in a patient with a T cell lymphoma linked to HTLV1

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Case description: Clinical findings
63 year-old woman
Adult T cell leukemia HTLV1+ without tumoral lymph node, diagnosed 6 years before and free of disease
Development of several nodular skin lesions of 2 to 6 cms, on the neck and in the axilla for 2 months
No fever, adenopathy or hepatosplenomegaly
Pain in pelvis
Biological findings
Hemogram:
10000 leucocytes/mm3 (2800 neutrophils, 5100 eosinophils, 1400 lymphocytes)
14.2 g/dl Hb
227000 Platelets/mm3
Immunophenotype of blood lymphocytes: clonal T cells CD3+, CD4+, CD7-.
PET scan of thorax, abdomen & pelvis
Several thoracic cutaneous & sub-cutaneous nodules
Large tumor near the uterine cervix and vagina (7x 6.5 x 6cms)
No thoracic or abdominal adenopathy
No hepatosplenomegaly
No bone lesions
skin biopsy and vagina biopsy
Biopsy fixation details: Skin biopsy and vaginal biopsies were fixed in formol.
Frozen tissue available: No
Details of microscopic findings:
Histological findings:
Huge abnormal infiltration of the whole skin dermis and the vagina mucosa by large lymphoid cells with round or irregular nuclei
Immunophenotype: IHC:
Abnormal cells are **CD20-, CD3+, CD5+, CD2+, CD7-, CD4+, CD8-, CD25+, CD30-/+, Ki67++**
Cytogenetics: No
Molecular studies: Clonal TCR rearrangement found on the skin biopsy on paraffin sections
Proposed diagnosis: Skin and Vagina localization of a T cell lymphoma linked to HTLV1
Interesting feature(s) of submitted case:
- **Skin tumors as an initial tumor occurring in a HTLV1 +ATLL patient free of disease**
- **Associated with a very rare large vaginal localization of HTLV1 +ATLL.**

EAHP18-LYWS-297

Extraosseus polypoid plasmacytoma of the cervix.

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Case description: We present a 37 year old female diagnosed of a cervical polyp in a rutinary gynecological exploration. Surgical removal of the polyp was carried out in June 2017. The histopathological diagnosis was of a solitary plasmacytoma of the cervix. The uterine cervix was rebiopsied in the nearby zone of the excised polyp in July 2017 and the diagnosis of plamacytoma was confirmed. To make the differential diagnosis of multiple myeloma, a series of laboratory tests were carried out. Complete blood count and urinalysis were normal, no monoclonal peaks were seen on immunoelectrophoresis on urine and blood samples. PET-TAC revealed no relevant lesions in bone or elsewhere. In September 2017 a partial excision-biopsy of the uterine cervix was done and revealed chronic cervicitis with sparse polytypic plasma cells. The patient is planning to keep her fertility options and decided no to recieve other treatment.

Biopsy fixation details: 10% buffered formalin.
Frozen tissue available: Not available.
Details of microscopic findings: A 5 mm polyp was submitted to the laboratory. The hematoxilin revealed a polypoid endocervical lesion filled with well differentiated plasma cells. Other type of lymphocyte were not found. Lymphoid follicles were absent.
Immunophenotype: The plasma cell expressed CD45, CD138, IgG and kappa light chains (95%). And were negative for CD20, CD56, IgM, IgA, IgD and cyclin d1. Light chain lambda was expressed in less than 5% of the cells.
Cytogenetics: Not done.
Molecular studies: DNA samples from the second biopsy were analyzed for clonality in IGH rearrangements using Biomed guidelines with gene scanning. We found monoclonality in the IGH segments Fr1, Fr2 and Fr3.

Proposed diagnosis: Extrosseus plasmacytoma of the cervix.
Interesting feature(s) of submitted case: Plasmacytomas of the cervix are extremely rare. Ten cases have been reported in the literature since 1949. Differentiation from plasma cell rich cervicitis were done with inmunophenotypical (light chain restriction) and molecular (IGH) techniques. Differentiation of a plasmacytoma from a marginal zone lymphoma with extreme plasma cell differentiation is almost imposible. Because of the rarity of this entity there is no known guidelines for treatment nor prognosis.

EAHP18-LYWS-306

CD138 Negative Plasmablastic Lymphoma: A Challenging Diagnosis

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Case description: A 63-year-old male with human immunodeficiency virus (HIV) infection presented with anal discomfort was found to have a large 6.6 X 5.2 X 4.6 cm fungating anal mass.
Biopsy fixation details: The tissue was fixed in 10% buffered formalin overnight and embedded in paraffin.
Frozen tissue available: NO
Details of microscopic findings: H&E stained histologic sections of the anal mass revealed diffuse infiltration by large atypical cells with round to oval nuclear contours, vesicular nuclear chromatin and prominent central nucleoli, and moderate amount of cytoplasm. Mitotic figures and apoptotic nuclear fragments were frequent. There was extensive necrosis.
Immunophenotype: The neoplastic cells were positive for CD45, MUM1, lambda, IgG, CMYC, OCT2 (subset), P53 (subset) and CD10, but negative for CD138, CD3, CD20, CD30, CD56, CD79a, kappa, ALK, EMA, CD79a, LMP1, HHV8, PAX5, CyclinD1, BCL2, BCL6, p40, AE1/AE3, HMB45, Melan A, S100, CK7, CK20, chromogranin. CD117 was equivocal. Ki67 was approximately 90%.
Cytogenetics: Not done
Molecular studies: Not done
Proposed diagnosis: plasmablastic lymphoma
Interesting feature(s) of submitted case: Plasmablastic lymphoma is a very aggressive lymphoma originally described in the oral cavity and frequently associated with HIV infection. The neoplastic cells are usually positive for CD138, MUM1 but negative or weakly positive for CD45, CD20 and PAX5. However, rare cases are negative for CD138. When they are negative for CD138, it can cause diagnostic challenges because they might morphologically resemble poorly differentiated carcinoma/ sarcoma and also lack the expression of CD3, CD20, CD45, CD79a, PAX5 and carcinoma/ sarcoma markers. Therefore, CD138 negative plasmablastic lymphoma is sometimes misdiagnosed as undifferentiated malignant neoplasm. We studied 20 cases of CD138 negative plasmablastic lymphoma from multiple institutes in the United States. We found that MUM1 is positive in 100% (15/15) cases; CD45 is positive in 43.8% (7/16), dim/ subset positive in 12.5% (2/16) and negative in 43.8% (7/16) of the cases; kappa or lambda light chain expression in 84.6% (11/13) cases while 15.4% (2/13) cases lack kappa or lambda expression; CD20 is negative in 94.1% (16/17)cases and focally positive in 5.9% (1/17) cases; PAX5 is positive in 13.3% (2/15), focally positive in 6.7% (1/15) and negative in 80% (12/15) cases; CD79a is positive in 13.3% (2/15), focally positive in 20% (3/15) cases and negative in 66.7% (10/15) cases; EBER is positive in 64.7% (11/17) and negative in 35.3% (6/17) cases. Most of the cases are from extra- oral cavity (95%, 19/20), including lymph node (40%, 8/20) and anus (10%, 2/20). 58.3% (7/12) patients are positive for HIV; 16.7% (2/12) patients had kidney transplant while 25% (3/12) patients have no definite history of immunodeficiency. CD138 negative plasmablastic lymphoma provides a diagnostic challenge for both hematopathologists as well as surgical pathologists. MUM1 and immunohistochemistry stains/ in situ hybridization for immunoglobulin light chains, EBER, B-cell receptor gene rearrangement study and a clinical history of immunodeficiency might help with the diagnosis. Molecular characterization of CD138 negative plasmablastic lymphoma might facilitate the diagnosis and shed light on the mechanism of this unusual entity.

EAHP18-LYWS-308

Pediatric high grade B-cell lymphoma of gastrointestinal tract

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Case description: 5 year old male presented with 5 month history of progressive, intermittent bloody diarrhea complicated by abdominal pain and recurrent emesis. Diagnostic studies during this time identified hypermobile cecum (UGI barium swallow study) and chronic recurrent ileocolonic intussusception (abdominal U/S, abdominal/pelvis CT with contrast, colononoscopy). Open laproscopy in May 2017 showed ileocolonic intussusception necessitating an ileectomy with identification of lymphoma on pathologic evaluation. Bilateral bone marrow and CNS evaluations were negative. The patient responded well to chemotherapy (COG Protocol ANHL1131, rituximab arm) with consolidation completed in September 2017. Post-consolidation PET/CT scan was negative and patient remains in remission, off therapy.
Biopsy fixation details: Fixed in formalin was a 7.0 cm x 4.2 cm ileal segment containing a 5.2 x 3.3 x 2.5 cm pedunculated, tan mass with serosal puckering.
Frozen tissue available: No
Details of microscopic findings: Microscopic findings: small intestine with submucosal mass composed of diffuse infiltrate of medium to large sized lymphoid cells with variable appearance. Some areas with cells having round to oval nuclear contours, multiple small nucleoli, scant to moderate cytoplasm; other areas with greater nuclear irregularity and variation in size, frequent single prominent nucleoli; numerous mitoses and apoptotic bodies; areas with interspersed macrophages imparting a 'starry sky' appearance.
Peripheral blood, bilateral bone marrow aspirates, touch preparation, clot and trephine biopsy sections (May 2007): mild hypochromic microcytic anemia; slightly hypocellular bone marrow (70%) with adequate trilineage hematopoiesis; negative for lymphoma
Immunophenotype: Immunohistochemistry (ileal lymphoma): Positive for CD79A, CD10, BCL6, CD43, CD45, Ki67 (~100%), CD20 (variable), MYC (variable). Negative for TdT, BCL2, CD34, CD3, CD5, CD30, ALK.
Immunohistochemistry (BM biopsy): few CD20+, PAX5+ small B-cells; no atypical large B-cells.
Flow cytometry (ileum): non-diagnostic due to poor specimen viability (10%)
Flow cytometry (bilateral bone marrow aspirates): no monoclonal B-cell population; 5% hematogones
Cytogenetics: FISH (ileal mass touch preparations and paraffin block):
POSITIVE for additional copy of BCL6 gene region in 22.5% of cells.
NEGATIVE for t(8;14)(q24;q32)MYC/IGH fusion; t(11;14)(q13;q32.3)CCND1/IGH fusion.
NEGATIVE for rearrangement of MYC, KMT2A (MLL) at 11q23, BCL2 and BCL6 gene regions.
No KMT2A gain identified.
Karyotype: no growth/failure
Molecular studies: EBV in situ hybridization (EBER): negative
Proposed diagnosis: High grade B-cell lymphoma with features of Burkitt lymphoma
Interesting feature(s) of submitted case: 1. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2016 recommends classifying pediatric high grade B-cell lymphomas (HGBCL) as BL or DLBCL, and not as HGBCL, NOS

2. This case has greater nuclear polymorphism than classic BL and is negative for MYC rearrangement

3. Cannot exclude MYC translocation with current FISH techniques; MYC-negative BL may have alternative mechanism involved in MYC dysregulation (BMC Cancer 2015;15:668)

4. Burkitt-like lymphoma with 11q aberration remains a possibility as FISH probes for CCND1 and KMT2A do not detect all cases (Am J Clin Pathol 2018;149:17-28; Virchows Arch 2017;471:453-466)

EAHP18-LYWS-314

Adult T-cell Leukemia/Lymphoma with Unusual Presentation of Small Bowel Obstruction

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Case description: A 41-year-old female from Jamaica presented to the Emergency Department with nausea, vomiting and abdominal pain. CT showed small bowel obstruction with retroperitoneal lymphadenopathy. A mid jejunum small bowel resection was performed and revealed several masses with the largest one measuring 5.1 cm in its greatest dimension.
Biopsy fixation details: The tissue was fixed in 10% buffered formalin overnight and embedded in paraffin.
Frozen tissue available: NO
Details of microscopic findings: H&E sections showed transmural infiltration by pleomorphic intermediate to large sized cells with irregular nuclei contours, vesicular chromatin, variably prominent nucleoli, and moderate amounts of cytoplasm. Mitotic figures and apoptotic bodies were frequently seen. Areas of necrosis were present.
Immunophenotype: Immunohistochemistry studies revealed the atypical cells were positive for CD2, CD3, CD4, CD5 (small subset, weak), CD25 (large subset), BCL2, MUM1, MYC (large subset) and are negative for CD7, CD8, CD20, CD21, CD10, BCL1, BCL6, CD30, LMP1, CD56, CD79a, TIA1, granzyme B. Ki-67 proliferation index is above 90%.
Cytogenetics: NO
Molecular studies: NO
Proposed diagnosis: Adult T-cell leukemia/ lymphoma
Interesting feature(s) of submitted case: With the patient's positive human T-cell leukemia-lymphoma virus 1 (HTLV1) infection status by Western Blot, it was most compatible with adult T-cell leukemia/lymphoma (ATLL). ATLL is a very rare lymphoma in the United States, consisting of only 0.2% in all registered lymphomas. Most patients are immigrants from Caribbean basin, Japan or central Africa. Most ATLL patients presented with leukocytosis, skin rash or lymphadenopathy. Although ATLL can occasionally involve gastrointestinal system, the presentation with bowel obstruction is very unusual. ATLL in the small intestine has to be distinguished from enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) and intestinal T-cell lymphoma, not otherwise specified (NOS). ATLL are mostly positive for CD4, CD25 and negative for CD7. The adjacent small intestinal mucosa usually has a relatively preserved normal architecture. EATL are usually CD4-/ CD8- and express cytotoxic granule-associated proteins such as TIA1, granzyme B and perforin. The adjacent intestinal mucosa usually shows features of celiac disease. MEITL are positive for CD8 and CD56 in the majority of cases and are frequently express T cell receptor gamma. Furthermore, the latter two entities have a negative result of HTLV1 testing. In summary, ATLL is very rare in small intestine. Patients from endemic areas with expression of CD4 and CD25, but negative for CD7 in the neoplastic cells raise the concern for ATLL. Confirmation of HTLV1 infection by serology helps with the final diagnosis and clinical patient management.

EAHP18-LYWS-315

Intravascular large B-cell lymphoma of the gastrointestinal tract: an unusual location of an uncommon lymphoma

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Case description: A 72-year-old woman with fungal skin infections and bacterial superinfection who was treated with topical and systemic antimicrobials developed a constellation of new symptoms including confusion, weakness, and ataxia. She was diagnosed with toxic megacolon. Pancolitis was seen on CT imaging, pseudomembranous colitis on sigmoidoscopy and C. difficile was positive. She developed signs of sepsis with organ dysfunction and underwent total colectomy with end ileostomy.

Biopsy fixation details: Formalin-fixed, paraffin embedded
Frozen tissue available: No

Details of microscopic findings: H&E sections of the colon show extensive multifocal patchy necrosis of crypts with accompanying eruptive karyorrhectic debris and associated profuse neutrophilic exudate alongside intervening areas of intact viable colonic mucosa, features supportive of pseudomembranous colitis. Intact crypts demonstrate marked acute inflammation. In both the colon and terminal ileum, vascular lumina are distended by large atypical cells with irregular nuclei, vesicular chromatin, prominent nucleoli and scant cytoplasm.

Immunophenotype: Immunohistochemical studies show that atypical cells are CD45(variable)+ CD79a+ Ki67(100%)+ MUM1(bright)+ CD30+ CD43+ and essentially negative for CD2, CD3, CD5, CD10, CD20, CD34, BCL6, TDT, PAX5, EBER1, HHV8 and ALK. Endothelial cells lining these spaces are podoplanin (D2-40)+.

Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Intravascular large B-cell lymphoma (involving colon and terminal ileum)
Interesting feature(s) of submitted case: Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma with growth restricted to the lumina of vessels, particularly capillaries, and occurs at an estimated frequency of less than 1 person per million. IVLBCL is aggressive, and without treatment is rapidly fatal. Known as a great mimic, most patients have advanced, disseminated disease at the time of diagnosis. Though the central nervous system and skin are the most common sites of involvement, virtually any organ can be involved, and the diagnosis is often delayed due to the non-specific and often confusing symptomatology. Gastrointestinal symptoms are infrequent, occurring in ~5% of cases, but actual GI presentation is very uncommon, with only rare cases reported.

IVLBCL cells typically express a full complement of B-cell antigens and have a profile consistent with an activated B-cell-like (ABC-like) histogenic origin. CD5 is evident in ~40% of cases. They typically lack cell surface proteins critical to lymphocyte transvascular migration, including CD29 (β1 integrin) and CD54 (ICAM-1), though neither of these is typically evaluated in the diagnostic setting. While most cases of IVLBL are of B-cell lineage, rare T-cell forms have been reported.

Interesting and unusual features in this case of IVLBCL are its:

1. Exceptional clinical presentation;
2. Apparent restriction of neoplastic cells to lymphatic spaces; and
3. Limited expression of B-cell markers.

EAHP18-LYWS-318

Intravascular large B cell lymphoma diagnosed in liver explant.

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Case description: The patient is a 69 year old man with cirrhosis secondary to hepatitis B and autoimmune hepatitis that was complicated by hepatocellular carcinoma. He underwent a liver transplant. His native liver showed chronic hepatitis with grade 2 activity and stage 4 fibrosis, no viable hepatocellular carcinoma, and intravascular large B-cell lymphoma (IVLBCL) involving the small vessels of the porta hepatitis. Immunostains showed the large neoplastic B-cells expressed BCL2 and MYC, consistent with a "double expressor" phenotype. Also of note, the large cells expressed BCL6 and lack CD10 and MUM1, consistent with a germinal center phenotype. BCL6 FISH was positive in 48 of 200 cells, while BCL2 and MYC FISH are negative. No lymphoma was found in the large porta hepatitis vessels, a nearby lymph node, or the liver explant. Six months after liver transplant, the patient died, and autopsy revealed no lymphomatous involvement of any of the organs sampled.
Biopsy fixation details: The liver explant was fixed in formalin.
Frozen tissue available: No frozen tissue is available.
Details of microscopic findings: Sections reveal two separate foci where large pleomorphic cells fill the lumens of small vessels in adipose tissue of the porta hepatitis. The neoplastic cells have large nuclei, irregular nuclear borders, occasional multinucleation, coarse chromatin, variably prominent nucleoli, and scant cytoplasm. Few mitoses are noted. No large cells are seen outside of the small vessels and the nearby porta hepatitis large vessels and lymph node are not involved. The liver explant shows chronic hepatitis with grade 2 activity and stage 4 fibrosis, but no lymphoma.
Immunophenotype: The malignant lymphoid cells express CD20, BCL2, BCL6 and MYC and lack CD30 and MUM1. EBV-in situ hybridization is negative. The neoplastic cells have a Ki67 proliferation index of 85%. CD3 is negative in tumor cells and stains increased background T-cells.
Cytogenetics: FISH studies demonstrate a BCL6 rearrangement in 48 of 200 cells. BCL2 and MYC are not rearranged.
Molecular studies: No molecular studies were performed.
Proposed diagnosis: Intravascular large B-cell lymphoma
Interesting feature(s) of submitted case: Intravascular large B-cell lymphoma (IVLBCL) is a rare B-cell lymphoma that has been described involving the vessels of a variety of tissues, including the liver. Involvement of liver explants is even rarer, and literature review reveals one prior case with a similar clinical presentation of a 51 year man with cirrhosis secondary to hepatitis C, an explanted liver with hepatitis and cirrhosis, and involvement of small hilar vessels by IVLBCL; in this case the neoplastic cells were non-germinal center type (CD10-, BCL6-) and biopsy of the patient's adrenal showed diffuse large B-cell lymphoma with an intravascular component. Our case shows the IVBCL is germinal center type (CD10 negative, BCL6 positive, MUM1 negative), a MYC and BCL2 "double expressor," and BCL6 rearranged by FISH. Autopsy follow up confirmed the absence of lymphomatous involvement of other organs. This case emphasizes the subtle morphological findings and the diverse clinical presentation of IVLBCL as defined by the current WHO classification. Given the lack of systemic findings in an immunosuppressed patient after 6 months of followup, this also raises the question of whether bona fide IVLBCL can be a localized indolent phenomenon associated with local factors such as hepatitis-associated inflammation.

EAHP18-LYWS-334

Intravascular large B-cell lymphoma of the brain

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Case description: A 28-year-old African man with history of sickle cell-beta thalassemia (HgbS/β-Thal (0+)) presented with gait abnormality and altered mental status. His gait changes worsened over the past 7 months. He also had nephrotic syndrome presumed to be secondary to focal segmental glomerulosclerosis. MRI and CT revealed multiple brain lesions concerning for demyelinating disease. He was given IV methylprednisolone with gradual improvement of his mental status and was discharged to acute rehab with a new diagnosis of multiple sclerosis. He represented from rehab 2 days later with fever and new onset confusion, aphasia and dressing apraxia. Brain MRI on readmission showed multiple scattered cerebral and cerebellar infarcts and numerous areas of signal abnormality in the brain. Overall, the MRI findings were non-specific but suggested an underlying vasculopathy. Brain biopsy was performed to rule out vasculitis. Following the brain biopsy bone marrow biopsy was performed for staging of the lymphoma.
Biopsy fixation details: The biopsy specimen was fixed in formalin.
Frozen tissue available: No.
Details of microscopic findings: Brain biopsy: H&E-stained sections showed fragments of dura and cortex with underlying white matter. Focal collections of large atypical mononuclear cells with irregular nuclei, vesicular chromatin, prominent nucleoli and scant cytoplasm filled and distended several small cortical and dural vascular spaces. Scattered mitoses were noted. Perivascular inflammatory cells, predominantly small lymphocytes, were also seen.
Bone marrow: sections showed hypocellular marrow involved by previously diagnosed lymphoma. There were aggregates of large neoplastic cells with intravascular localization. The neoplastic cells accounted for the majority of the cellularity.
Immunophenotype: Brain biopsy: Immunohistochemical stains performed with adequate controls showed that the neoplastic cells were CD20+ CD79a+ CD5+ BCL2+ BCL6+ MUM1+ B cells. The neoplastic cells are negative for CD10, TDT, CD30, and EBER. Perivascular and scattered small CD3+ CD5+ T cells were also present. The neoplastic cells were located within vascular spaces that were positive for CD31, CD34, and D2-40 (focal). The Ki-67 proliferation index was approximately 100%.
Bone marrow: Immunostains performed on the biopsy core with adequate controls show the large atypical cells are CD20+ CD79a+ BCL6+ (subset) MUM1+(subset) B cells, with similar phenotype to the brain biopsy.

Cytogenetics: Cytogenetic studies were performed on the bone marrow aspirate. Conventional karyotype showed following findings:
75~86,XXYY,+del(X)(q22q24),-1,-2,-2,t(3;6)(p21;q31)x2,add(4)(q21),-5,add(6)(q12)x2,+add(6)(q25),-7,t(7;21)(q11.2;p11.2)x2,-8,-8,add(?9)(q12)x2,+10,-15,-16,-17,+18,add(18)(q12),-19,add(19)(p13.1),+2~7mar[cp11]/46,XY[10]
Molecular studies: Not performed.
Proposed diagnosis: Intravascular large B-cell lymphoma
Interesting feature(s) of submitted case: Clinical presentation with numerous unspecific CNS symptoms in a patient with sickle cell-beta thalassemia, extensive bone marrow involvement and complex karyotype.

EAHP18-LYWS-364

Primary skin extranodal NK/T cell lymphoma, NOS with abnormal immunphenotype (CD8+/cytotoxic molecules+/CD56-/CD20+)

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Case description: The patient is a 64 years-old man who is admitted with a 2.5 cm nodular lesion on his right knee. He noted that this lesion was present for 2 years, but its diameter was increased in lately. He had no B symptoms, lymphadenopathy or hepatosplenomegaly. Hemogram was normal. After the diagnosis of primary cutaneous lymphoma, bone marrow biopsy was carried out but there was no involvement by lymphoma. After 10 months and 43 months later from the diagnosis, there occurred two recurrent lesions on his buttock and right knee again, respectively. The diagnosis and immunohistopathological findings were same with the initial biopsy. The patient received radiotherapy and chemotherapy. He is alive and doing well for 50 months without systemic involvement.
Biopsy fixation details: Formalin fixed paraffin embedded tissues
Frozen tissue available: No.
Details of microscopic findings: There was a dense dermal diffuse or perivascular/periadnexial, nonepidermotropic infiltrate with grenz zone. Neoplastic cells had medium or large size irregular nuclei, scant cytoplasm, and a few nucleoli.
Immunophenotype: The neoplastic cells were positive for CD3, CD8, EBER, bcl-2, TIA-1, and granzyme. CD20 was strongly positive in sparse B cells and moderate/weak in neoplastic T cells. CD2, CD4, CD5, CD7, CD56, CD57, ALK, EBV-LMP-1, CD123, CD25, TdT, MPO, CD34, CD79a, PAX-5, OCT-2, CD10, bcl-6, CD30 were negative. Ki67 was 90% in the neoplastic cells.
Cytogenetics: TCR clonal.
Molecular studies: Not done.
Proposed diagnosis: Primary skin extranodal NK/T cell lymphoma, NOS with abnormal immunphenotype (CD8+/cytotoxic molecules+/CD56-/CD20+)
Interesting feature(s) of submitted case: The case was diagnosed as extranodal NK/T cell lymphoma, NOS based on EBER positivity alone. The other immunophenotypic features of the case were very unusual such as cytotoxic phenotype, negativity with CD56 and weak positivity for CD20. Although he has third recurrence, the patient is very well for now.

EAHP18-LYWS-374

De novo plasmablastic lymphoma of testis

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Case description: A 53-year-old previously healthy male presented with fatigue and a 2-month history of a left testicular mass. The patient was initially treated with antibiotics (x 2 week) without resolution of the enlargement. Ultrasound of scrotum revealed a solid mass measuring 10.0 x 5.0 cm. He did feel increased swelling in his left extremity for the past weeks but denied fevers, chills, or weight loss. He also denied any lifetime use of IV drugs or homosexual behavior. Physical examination did not reveal any generalized lymphadenopathy or hepatosplenomegaly. Laboratory study showed his PSA level was within normal range (1.8) and negative for HIV infection. CBC data was within normal range. A staging bone marrow biopsy shows no evidence of malignancy. A left orchiectomy was performed. The specimen was submitted for pathologic examination.
Biopsy fixation details: 10% formalin
Frozen tissue available: No.
Details of microscopic findings: The specimen consists of an enlarged testis with attached epididymis and spermatic cord. On sectioning, the parenchyma of the testis appears to be totally replaced by a tumor which measures 7.0 x 4.5 x 4.5 cm. Microscopic examination showed well encapsulated testicular mass composed of sheets of atypical lymphoid cells with immunoblastic and focally plasmablastic features intermingled with sparse small lymphocytes. The neoplastic cells are large in size with round to oval nuclei, one centrally located prominent nucleus, and abundant of amphophilic cytoplasm. Increased apoptosis and focally active mitosis are observed.
Immunophenotype: Immunoperoxidase stains are performed with appropriate positive and negative controls. The neoplastic cells stain diffusely positive for CD79a, CD43, CD138 and MUM1. In situ hybridization (ISH) with kappa and lambda light chain probes are predominantly negative and no discrete clonality is identified. The cells are negative for CD20, PAX-5, CD56, CD117, CD30, HHV-8, bcl-2, bcl-6, CD3, CD10, and cytokeratin cocktails (AE1/AE3/CAM 5.2). A subset of the cells expresses CD45. CD20 highlights the background small B-lymphocytes. The proliferation index by ki-67 is estimated at 90%. Epstein Barr virus (EBER) ISH is positive within the neoplastic cells.
Cytogenetics: NA
Molecular studies: NA
Proposed diagnosis: Plasmablastic lymphoma of testis
Interesting feature(s) of submitted case: The prototypic plasmablastic lymphoma (PBL) occurs in HIV positive patient with a mass found in head and neck region, in particular oral cavity. Involvement to gastrointestinal tracts is the second most common site followed by skin. PBL is rarely found in other organ or tissue such as bone, liver, lung, CNS, orbits, nasal cavity or paranasal cavity. Cases with genitourinary tract involvement including testicular PBL are extremely rare. Given a rarity of PBL in testis of HIV negative individual while seminoma and diffuse large B-cell lymphoma are the two most common neoplasms in the location and their morphological resemblance to PBL, a comprehensive immunohistiochemical work-up is necessary before rendering a final diagnosis. Lack of CD45, kappa and lambda light chain expression could lead to incorrect diagnosis.

EAHP18-LYWS-391

53 year-old man with lesions involving cerebral parenchyma and bilateral adrenal glands

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Case description: 53 years old female presented to a local ER after having a syncope episode at work. This was considered to be likely a vasovagal episode or due to dehydration from an infection. One month after, she developed altered mental status and was readmitted to the hospital. MRI of the brain revealed multifoci of hemorrhagic lesions involving bilateral frontal and parietal lobes and R temporal lobe. A CT scan of abdomen showed bilateral ill-defined adrenal masses concerning for metastasis but no lymphadenopathy or hematosplenomegaly. The biopsies of brain and L adrenal gland were performed (results see below). The patient was transferred to our hospital. A bone marrow biopsy and a lumbar puncture were conducted for staging, which were negative for malignancy. The patient was started on therapy with methotrexate and Rituxan followed by CHOP and has achieved partial remission.
Biopsy fixation details: Formalin 10%
Frozen tissue available: No
Details of microscopic findings: The brain biopsy shows predominantly intravascular accumulation of large atypical lymphoid cells with vesicular chromatin, prominent nucleoli and abundant amphophilic cytoplasm. Some neoplastic cells display atypical mitosis. The submitted H & E sections of biopsy of L adrenal gland show that numerous large atypical lymphoid cells are packed in intravascular channels. Patchy extravascular involvement is also observed. Deep sections show focally large cells in sheets.
Immunophenotype:
Immunohistochemical stains are performed with appropriate positive and negative controls. In the sections from brain biopsy the large atypical lymphoid cells are positive CD20, and CD5, and negative for pancytokeratin, CD3, and CD10. CD31 highlights vasculatures. Ki67 stain highlights >95% of the atypical B-cells. In the section of adrenal biopsy these intravascular large atypical lymphoid cells stain positive for CD20, CD5, BCL-6, weak BCL-2 and MUM1 and negative for CD3 and CD10. The proliferation rate by Ki67 is estimated at 80-90%. Per report, the flow cytometry performed on the adrenal biopsy revealed a small population of clonal B-cells coexpressing CD5, FMC-7 and HLA-DR.
Cytogenetics: NA
Molecular studies: NA
Proposed diagnosis: Intravascular large B-cell lymphoma (IVLCL) involving cerebral parenchyma and CD5 positive DLBCL in adrenal gland
Interesting feature(s) of submitted case: IVLCL is a rare but aggressive subtype of extranodal non-Hodgkin lymphoma characterized by exclusively intravascular growth pattern and involving more than one system such as skin, liver, spleen, bone marrow and rarely adrenal glands. Coexpression of CD5 or CD10 is identified in a subset of IVLCL cases (38% and 13%, respectively). MUM1 is usually positive in CD10 negative case. The biopsy of brain tissue from our patient showed typical intravascular large B-cells coexpressing CD5. Interestingly, the biopsy of left adrenal gland showed the lymphoma cells were not only found intravascular channels but also presented in the adjacent tissue, focally in sheets in the deep sections. The latter raises a concern about de novo CD5+ diffuse large B-cell lymphoma (DLBCL) as a subset of such cases (19-38%) could show intravascular and sinusoidal growth pattern (Yamaguchi 2008 and Orwat and Batalis 2011). Per WHO minimal extravascular infiltrate is allowed for IVLCL and recurrences (in CNS) may lead to extravascular mass. However, it is difficult for us to determine the adrenal lesion in our patient is from a solid mass (DLBCL) or only focal extravascular invasion (IVLCL). Limited biopsy material also precludes a further exploration of clonal relationship between brain and adrenal lesions.

EAHP18-LYWS-437

Plasmablastic lymphoma with aberrant CD3 expression

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Case description: 76-year-old man with history of diabetes, coronary artery disease, hypertension, gout, and glaucoma presented with several days of hematuria.
CBC: WBC 7.8 K/uL, HGB 11.7 g/dL, PLT 257 K/uL.
Biopsy fixation details: Formalin fixation.
Frozen tissue available: No frozen tissue available.
Details of microscopic findings: Sheets of large atypical cells are present with abundant cytoplasm and variably prominent nucleoli. Other areas show more mature plasma cells.
Immunophenotype: The large cells are positive for CD3, CD4, CD138, MUM1 and kappa light chain (in situ hybridization). EBER (in situ hybridication for Epstein-Barr virus) is positive. The cells are negative for CD20, PAX-5, CD79a, CD30, CD5, CD7, CD8, HHV8, ALK, and lambda in situ hybridization.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Plasmblastic lymphoma.
Interesting feature(s) of submitted case: This case is interesting because it had strong CD3 and CD4 expression. T-cell markers can be expressed in plasmablastic lymphoma/plasmablastic plasma cell myeloma. We have encountered two cases with CD3 expression in the past several months. CD3 was recently reported in a series of 17 cases by Pan and colleagues (2018). CD4 has also been reported in the literature. This can be a diagnostic pitfall, especially if more than one T-cell marker is present, leading to a misdiagnosis of peripheral T-cell lymphoma, NOS.

EAHP18-LYWS-438

Extranodal NK/T cell lymphoma, nasal type with initial cutaneous presentation

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Case description: A 55 year old woman with a history of Systemic Lupus Erythematosus (SLE) presented in 10/2007 with a rapidly enlarging calf ulcer. She was originally diagnosed with SLE two years prior when she presented with a malar rash and polyarthritis. 6 months following her SLE diagnosis, she developed skin lesions on her calf which were diagnosed on biopsy as lymphocytic vasculitis. 4 months later, one of these lesions began to ulcerate, and was clinically called pyoderma gangrenosum. No biopsy was performed. This calf ulcer progressively enlarged over the ensuing year, in spite of treatment with immunosuppression and antibiotics. On this admission, she was found to have a 15 cm calf ulcer which was biopsied and submitted to surgical pathology. Two days into her admission, before a diagnosis had been rendered on the skin biopsy, she was noted to have facial edema, CN VII palsy, and a necrotic mass visible in the left nostril. This mass was biopsied. In light of the results of both biopsies, the prior biopsy from 7/2006 was re-reviewed.
Biopsy fixation details: Formalin
Frozen tissue available: No
Details of microscopic findings: Skin biopsy (11/2007) shows an infiltrate of small to medium sized irregular lymphocytes within the dermis and subcutis with focal extension into the epidermis. There is extensive necrosis and angioinvasion.
Biopsy of the nasal mass (11/2007) shows ulcerated and necrotic sinonasal mucosa with a dense infiltrate of medium sized irregular lymphocytes with inconspicuous nucleoli and scant cytoplasm. There is again evidence of angioinvasion and extensive necrosis.
A retrospective review of the patient's skin biopsy from 1.5 years prior (7/2006) reveals an angiocentric dermal infiltrate of small mature lymphoid cells with focal fibrinoid necrosis of small vessels and dermal necrosis. (Diagnosed as lymphocytic vasculitis).
Immunophenotype: Neoplastic cells are positive for EBER, CD3, CD30, CD43, CD56, TIA1, and UCHL1, while negative for CD5, CD4, CD8, CD57, and LMP1. Ki-67 ~60% of cells.
Cytogenetics: NA
Molecular studies: NA
Proposed diagnosis: Extranodal NK/T cell lymphoma, nasal type
Interesting feature(s) of submitted case: This is an interesting case of an extranodal NK/T cell lymphoma, nasal type, which presented initially with skin lesions in a patient who was later found to have a sinonasal mass. Although this lymphoma classically presents in the nasal cavity, as the name implies, skin lesions are not uncommon and in some cases may be the only manifestation. In this case, the microscopic appearance of the dermal infiltrate was deceptively bland, especially in the retrospectively analyzed biopsy from earlier in the patient's course. However, the gross appearance of the patient's leg ulcer, not known to the pathologist at the time of the biopsy, certainly suggested an aggressive process. This case highlights the potential for misdiagnosis when extranodal NK/T cell lymphoma first presents outside of the nasal cavity. In this case, it was only the CD5 negativity in the dermal lymphoid cells that raised the suggestion of a neoplastic process, as the cells morphologically were predominantly small with only mild atypia and in a background of mixed inflammation. This patient's case was complicated by her history of SLE. Many connective tissue diseases manifest in the skin, and several, including SLE, can present with perivascular dermal infiltrates and/or vasculitis. The distinction between a neoplastic and inflammatory infiltrate may be obvious in some cases when the infiltrating cells are large, atypical, and without background inflammation, but one must maintain a high level of suspicion even when this is not the case.

EAHP18-LYWS-450

Intestinal B-cell non Hodgkin lymphoma in HIV patient with partial features of extracavitary PEL

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Case description: A 27-year-old men, diagnosed with HIV infection diagnosed in 2013 was treated with antiretroviral therapy. At this time, he also was diagnosed with atypical mycobacteriosis in a lung biopsy, and disseminated Kaposi's sarcoma. He received 5 cycles of chemotherapy (liposomal doxorubicin). In july 2017, the patient was admitted to the hospital with abdominal pain and gastrointestinal bleeding. Endoscopic examination revealed an ulcer and tumor in the duodenum and biopsies were taken. The laboratory tests showed Hb 6.9 g/dl, DHL 275 UI/L, CD4: 241 cells/mm^3, a CT-scan showed hepatosplenomegaly. After the diagnosis, he received 4 cycles of EPOCH, with partial response.
Biopsy fixation details: 4% Buffer formalin
Frozen tissue available: Not available
Details of microscopic findings: Histological examination showed intestinal mucosa with a diffuse lymphoid infiltration in the lamina propia, characterized by pleomorphic large cells, with immunoblastic or anaplastic cytology with frequent involvement of endothelial-lined lymphatic channels, resembling and intravascular dissemination.
Immunophenotype: The neoplastic cells were positive for CD3, MUM1, Ki67 (95%), MYC, EBER-ISH and HHV-8. The cells were partially positive for CD4, and TIA1, and negative for CD20, CD79a, CD19, PAX5, CD2, CD5, CD7, CD8, CD138, CD38, BCL6, FOXP3, PD1, CD10, CD34, BCL-2, CD30, CD56. The D2-40 stain revealed a clear-cut intra-lymphatic dissemination pattern.
Cytogenetics: Not available
Molecular studies: In process (IGH by PCR)
Proposed diagnosis: Extracavitary, primary effusion lymphoma (PEL) with aberrant expression of T-cell markers
Interesting feature(s) of submitted case: PEL is the least common lymphoma subtype observed in HIV+ patients (1-3%). Extracavitary PEL has similar morphological and phenotypic features but presents with solid masses in extranodal sites, mainly in gastrointestinal tract like in our case. The viral coinfection (HHV8/EBV) observed in 90% of the cases, and the location in this case suggest the diagnosis of extracavitary PEL. A rather unusual finding was the dissemination of the tumor cells in the lymphatic channels. The lack of expression of B-cell markers and the aberrant expression of T-cell markers (CD3) is rather characteristic. Nevertheless, it has been reported that extracavitary PEL expresses B-cell associated markers (CD20, CD79a, CD138) slightly more often than PEL (25%). In conclusion, this case represents an example of extracavitary PEL. The aberrant expression of T-cell markers in this entity, although well described, represents always a diagnostic challenge, especially in the intestine, where T-cell lymphomas are not infrequent.

EAHP18-LYWS-476

Cutaneous type adult T cell lymphoma/leukemia can mimic mycosis fungoides both clinically and pathologically--diagnostic pitfalls.

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Case description: This 70-year-old female had skin rash, including wheals, erythematous nodules on right forearm and erythematous patches on the trunk for three or four months. It attacked several times a week. She visited our Dermatology clinic in February 2017. Hypersensitivity reaction or chronic eczema was the first clinical impression. Local steroid cream was prescribed. But, the lesions didn't improve much. One month later, the lesions persisted and skin biopsy was done to clarify the diagnosis. Besides these, she didn't have any relevant past history. Hemogram showed mildly elevated white blood cell counts (11.6 K/uL) and differential counts (Segment: 77.0%, Eosinophil: 0.6%, Basophil: 0.2%, Monocyte: 9.5%, Lymphocyte: 12.7%). Peripheral blood flow cytometry reported no evidence of lymphoma/leukemia. Anti-HTLV- I/II antibody was positive (3.35; Reference: < 0.310) and HIV-1 western blot was negative. There was no significant abnormality in the chest and whole abdominal CT evaluation.
Biopsy fixation details: fixed in 10% neutral buffered formalin.
Frozen tissue available: Not available.
Details of microscopic findings: Section shows skin tissue with a diffuse dermal lymphocytic infiltration with focal epidermotropism and focal crush artifact. The lymphocytic infiltrate is more prominent in the upper dermis with extension to around the skin appendages. The infiltrate comprises of small to medium to occasional large cells with vesicular nuclei and nucleoli. Focal granulomatous inflammation with epithelioid histiocytes engulfing dermal collagen with formation of multinucleated giant cells is discernible. The epidermotropic lymphocytes range from small to medium to rare large cells, forming focal Pautrier microabscess-like lesions.
Immunophenotype: Immunohistochemical study shows that the atypical lymphocytes express CD2, CD3, CD4, CD25, and MUM1 but not CD7, CD8, CD20, CD30, CD68, TIA-1, or granzyme B. The labeling index by Ki67 immunostaining is at around 40-50%. Stainings with CD8, TIA-1, and granzyme B highlight many reactive cytotoxic small lymphocytes, which are not the tumor component.
Cytogenetics: Not available.
Molecular studies: PCR analysis for DNA of HTLV-1 TAX shows a positive result, indicating integration of the proviral DNA into the tumor cells (done by Prof. Koichi Ohshima, Kurume University, Kurume, Japan.)
Proposed diagnosis: Adult T cell lymphoma/leukemia, cutaneous type or smoldering type.
Interesting feature(s) of submitted case: The patient had erythematous skin rashes and nodules on right forearm and erythematous patches on the trunk for three or four months. The skin lesions were resistant to topical steroid treatment and the clinical impression of our dermatologist was mycosis fungoides. It also mimics mycosis fungoides pathologically due to presence of Pautrier's-like microabscess and halo cells in the epidermis, granuloma in the dermis and overlapping immunophenotypes. Without thinking of the possibility of adult T cell lymphoma/leukemia and doing anti-HTLV-1 antibody test, it can be misdiagnosed as granulomatous mycosis fungoides.

EAHP18-LYWS-525

Diffuse telangiectasias: a red flag for an aggressive lymphoma?

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Case description: A 63-year-old female was analysed for B-symptoms that presented six months earlier. During hospitalization, she developed telangiectasias all over her body. Standard laboratory blood tests demonstrated an increased LDH (477U/L) and erythrocyte sedimentation rate (80mm/hr), and a low hemoglobin (6.3mmol/L). Blood serology and PCR were negative for HIV, hepatitis A, B, C and E, and parvovirus B19. Also, blood cultures and QuantiFERON-TB were negative.

Histologic examination of a skin biopsy of the leg showed dilatation of the dermal and subcutaneous blood vessels, with clustering of large, blastic cells with prominent nucleoli within the lumina of the blood vessels and scattered apoptotic figures. Immunohistochemistry demonstrated that these cells were positive for CD20, BCL6, MUM1, BCL2, IgM, MYC, and CD5 (very weak) and negative for CD3, CD10, Cyclin D1, and CD30. The proliferation fraction was nearly 100%. In situ hybridization for Epstein Barr virus early RNA (EBER-ISH) was negative. The histologic diagnosis was an **intravascular large B-cell lymphoma** (IVLBCL).

Further staging examination revealed no signs of the neoplastic lymphoid population in the bone marrow. Ultra sound of the abdomen and a CT-scan of the thorax and abdomen were without abnormalities. A PET/CT scan showed one marginally enlarged lymph node in the mediastinum with FDG uptake. Cytology of this lymph node identified large, blastic B-cells with a corresponding immunophenotype as the tumor cells in the skin. An MRI of the brain was without signs of cerebral involvement, as was confirmed by a lumbar puncture. Consequently, this IVLBCL with disease involvement of the skin and a mediastinal lymph node was classified as Ann Arbor stage IV.

Next, the molecular make-up of the IVLBCL was elucidated. Fluorescence in situ hybridization (FISH) revealed no rearrangements of MYC, BCL2, and BCL6. Targeted Next Generation Sequencing (NGS) showed mutations of MYD88 L265P (NM_001172567) and CD79B Y196F (NM_001039933).

The patient was treated with six courses of R-CHOP with complete remission of her skin lesions and B-symptoms and a normal PET/CT scan. However, quickly after completion, she again developed B-symptoms and telangiectasias. A new skin biopsy revealed a relapse of her IVLBCL. At this point, a liquid biopsy was performed using digital droplet PCR and the MYD88 L265P mutation was detected in the cfDNA in her blood. In second line, she was treated with R-DHAP. A few days after the first course, she developed a neutropenic fever due to an E. coli urosepsis with progression to multi-organ failure. Despite maximal further treatment at the ICU, the patients deceased seven months after diagnosis.

Biopsy fixation details: FFPE
Frozen tissue available: Yes
Details of microscopic findings: See case description
Immunophenotype: See case description
Cytogenetics: -
Molecular studies: See case description
Proposed diagnosis: Intravascular large B-cell lymphoma
Interesting feature(s) of submitted case: Our molecular approach identified mutations in MYD88 and CD79B in this patient with an IVLBCL, of which the mutational profile is currently unknown. We were able to demonstrate that these mutations are a recurrent finding in a series of 25 IVLBCL patients (unpublished work). This is not only interesting for improving our understanding of lymphomagenesis of IVLBCL, but also for the identification of targets for novel molecular therapies, such as the BTK-inhibitor ibrutinib, for these patients. In addition, liquid biopsy may not only be helpful as an additional diagnostic tool but may also be used as a marker that may predict treatment response and/or early relapses in these patients.

EAHP18-LYWS-531

Multiple metachronous cutaneous monoclonal B-cell proliferations as harbingers of systemic angioimmunoblastic T-cell lymphoma

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Case description: A 66 year-old man presented with a solitary violaceous plaque on the left shoulder. A biopsy was interpreted as cutaneous marginal zone lymphoma. Thorough staging was negative for additional cutaneous lesions or extracutaneous disease. This lesion spontaneously regressed. Over the ensuing 11 months he developed additional cutaneous nodules and then systemic lymphadenopathy. A lymph node biopsy showed composite angioimmunoblastic T-cell lymphoma and diffuse large B-cell lymphoma. He received multiagent systemic chemotherapy but died of systemic lymphoma 19 months from initial presentation.
Biopsy fixation details: Formalin.
Frozen tissue available: No.
Details of microscopic findings:
1. Initial diagnosis, skin of left shoulder skin punch biopsy(tissue block depleted see Power Point images) showed a dense infiltrate of mostly small lymphocytes arranged in rounded nodules within the dermis and superficial subcutis. Large lymphocytes and plasma cells were a minority of the cells. Secondary lymphoid follicles were present and surrounded by increased numbers of plasma cells. EBV (EBER1) ISH was positive in tumor cells.
2. Eleven months after initial diagnosis, right axillary lymph node biopsy (slides submitted to workshop) showed effacement of the architecture by a diffuse, polymorphic infiltrate of small, intermediate and large cells with variable numbers of clear cells, eosinophils and proliferations of arborized vasculature.
Immunophenotype:
1. The majority of lymphocytes were of B-cell lineage expressing CD20, CD79a with monotypic λ light chain restriction. These cells were negative for CD5, CD10 and BCL6. CD30 stained a few scattered immunoblasts. CD3-positive mature T-cells were a minority of cells and without nuclear atypia.
2. There were two clearly identifiable proliferations within this node. One showed typical histology and immunophenotype of angioimmunoblastic T-cell lymphoma with tumor cells positive for CD3, CD4, CD5, CD10 and PD-1. CD21 highlighted aberrant follicular dendritic cell proliferations. The other proliferation comprised sheets of large, pleomorphic B-cells expressing CD79a, CD30 and lambda and but negative for CD20 due to therapeutic effect. EBV (EBER) ISH was negative.
Cytogenetics: None
Molecular studies: Please see Power Point slide for summary table. Briefly, the specimen from the initial skin biopsy showed a monoclonal IGH gene rearrangement and a polyclonal TRG gene rearrangement. Three of four subsequent biopsies identified an identical monoclonal TRG gamma rearrangement. Two of the four specimens also showed monoclonal IGH rearrangements that were neither identical to one another nor to the original IGH gene rearrangement, indicative of unique B-cell clones.
Proposed diagnosis:
1. EBV+ B cell lymphoproliferative disorder mimicking primary cutaneous marginal zone lymphoma.
2. Angioimmunoblastic T-cell lymphoma and diffuse large B-cell lymphoma.
Interesting feature(s) of submitted case:
1. Three metachronus immunophenotypically and genetically distinct, monoclona cutaneousl B-cell neoplasms.
2. Variablility of EBV association throughout multiple biopsies.
3. Cutaneous B-cell-rich and even clonal B-cell infiltrates may mask underlying or evolving systemic T-cell lymphoma. Therefore, we recommend looking for eosinophils and performing EBV ISH on all atypical or neoplastic cutaneous lymphoid proliferations as a clue to the systemic T-cell lymphomas with secondary B-cell proliferations.

EAHP18-LYWS-534

NK/T-cell lymphoma suffering recurrenced as intestinal ulcers and involving bone marrow and peripheral blood.

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Case description: A 52–years old Chinese woman came to our hospital complaining from fever, weight loss and headache. A head and neck CT study revealed a mass in the nasal cavity that disrupted osseous tissue. A diagnosis of NK/T-cell lymphoma nasal type was rendered (2015). She received 6 cycles of SMILE as well as localized radiotherapy reaching a complete response. Two years later (2017) several superficial ulcers along the large bowel were found in a routinary colonoscopy. Biopsies were taken and diagnosed of infiltration by NK/T-cell lymphoma. Interestingly, at that time, scattered EBER-positive cells were found in the bone marrow biopsy on peripheral blood smears. Flow cytometry studies of peripheral blood identified two different T-cell populations ; the neoplastic T-cells and an expanded population of CD8-positive T-cells. NGS of both intestinal neoplastic tissue and peripheral blood sample identified the same clonal population. EBV viral load were high at diagnosis and during the whole disease period. Double positive cells in previous endoscopy biopsies (CD3/EBER) taken in 2013, were seen.
Biopsy fixation details: Tamponed Formallin 10%
Frozen tissue available: Not available
Details of microscopic findings: Large atypical cells with irregular nuclei were found in nasal mucosae, large intestinal bowel and peripheral blood.
Immunophenotype: Neoplastic cells expressed CD3, PERFORIN, GRANZYME B, TCRBETA and EBV (EBER). They were also partially CD8-positive and weakly CD56-positive.
Cytogenetics: Not done
Molecular studies: Next Generation Sequencing (NGS) of TCRGAMMA gene
Proposed diagnosis: **NK /T-cell lymphoma suffering recurrenced as intestinal ulcers and involving bone marrow and peripheral blood in the setting of a indolent chronic EBV-positive lymphoproliferative process**
Interesting feature(s) of submitted case: - A nasal-type NK/T-cell lymphoma in the setting of a indolent chronic EBV-positive lymphoproliferative process has been diagnosed. Clinical, histological and serological studies confirm the presence of an indolent EBV-positive systemic disorder with gastric mucosa involvement.
- Tumour relapses again as an indolent disorder, with infiltration of intestinal mucosa, bone marrow and peripheral blood .
- TCR clonallity present in an NK/T-cell lymphoma has been described but is rare. NGS will be usefull to follow-up and discrimination of small populations of neoplastic cells among a high polyclonal background .

EAHP18-LYWS-552

Primary dural marginal zone lymphoma mimicking meningioma

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Case description: A 59 year- female presenting with headache and tinnitus was submitted to the hospital. There was no sign of systemic disease by radiological and laboratory experiments. There was no monoclonal gammapathy in the serum. A magnetic resonance imaging scan revealed a cystic falx-based tumor 3.5 cm in greatest dimension located in the right parietal lobe extending to the pariteal bone. The tumor was resected. Local radiotherapy performed. Two years after the diagnosis the recurrence was seen. The patient had received 6 courses of anti CD20 therapy. She is under follow up without any recurrence.
Biopsy fixation details: 10% neutral buffered formalin.
Frozen tissue available: Not available.
Details of microscopic findings: The tumor involving the dura, parietal bone were composed of diffuse infiltration of atypical small lymphoid cells. The infiltration was composed of plasma cells and lymphoid cells which had narrow eosinophilic cytoplasm and small hyperchromatic nuclei. Some of these cells had significant nucleolus. Mitotic activity was infrequently seen.
Immunophenotype: Immunohistochemically, the lymphoid cells were positive for CD45, CD20, Pax5, and focally IgM. There were plasma cell aggregates expressing CD38 and MUM1 which were kappa monotypic. Ki-67 proliferation index was determined %20. The neoplastic cells were negative with Lambda, Bcl-6, CD56 and HHV-8.
Cytogenetics: Not performed.
Molecular studies: EBER by in situ hybridisation was negative. MYD88 mutation analysis is pending
Proposed diagnosis: Primary dural marginal zone lymphoma with IgM kappa monotypic plasma cell differentiation
Interesting feature(s) of submitted case: We would like to share our case, since it has an indolent disease course with high cure potential, and primary dural marginal zone B-cell lymphoma is very rare, with only a few reported cases worldwide.

EAHP18-LYWS-553

Primary Cutaneous T-cell prolymphocytic lymphoma

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Case description: Introduction. Primary Cutaneous T-cell prolymphocytic lymphoma/leukemia (PCTPLL) representing approximately 20% of the cases in adults over the age of 30. Involvement of the peripheral blood, bone marrow, lymph nodes, liver, spleen, and skin can occur. The clinical course is typically very aggressive with poor response to conventional chemotherapy and short survival rates.
History. A 58-year-old female presented with erythematous papules, macules, and plaques with desquamation all over the body, sweating, fever 38º (May 2010). Her primary care physician initially suspected psoriasis but without an effect of treatment: there were seals in the skin (Jan 2011). Her past medical history was marked by type 2 diabetes and no current medications in use. Biopsy results confirmed PCTPLL.
She does not currently smoke and drink alcohol.
Physical examination. Patients complained of rash and seals on the skin of the body and head, severe general weakness, high temperature, and itching. We observed a lot of cutaneous purple painful plaques and nodules with different diameter (on the ears too). They were deeply infiltrated into the subcutaneous fat. On general examination (Feb 2011) we noticed bilateral palpable superficial lymph nodes on the axillary, cervical, and inguinal areas.
Laboratory data. Blood samples: anemia (Hb 11.0 gm/dl), WBC count 29 × 10^3/ml, LDH 1582 U/l. Bone marrow aspirate: elevated levels of immature and mature eosinophils. Identify lymphoid cells medium and large size about 6%. Flow cytofluorimetry: were not found the monoclonal proliferation of T or B lymphocytes. The whole body CT-scan was performed at the same period enlargement of all groups of lymph nodes 30-45-58 mm.
Treatment. The therapeutic strategy was chosen by international and local treatment guidelines. This patient was not eligible for bone marrow transplantation. The patient received CHOEP x8 (Mar-Aug 2011) regimen as first-line treatment. Partial response and complete response were achieved after the 4th and 8th cycle of Chemotherapy, respectively.
Outcomes: The Patient is still in remission. She has solitary hyperpigmented macules with clearing in the center on the skin of legs.
Biopsy fixation details: For biopsy fixation, we used standard 10% neutral buffered formalin (NBF).
Frozen tissue available: The frozen tissue has not been done.
Details of microscopic findings: The skin biopsy of plaques and nodules have been done and sent for evaluation in the Pathological histology department. In the biopsy material, there are skin fragments with diffuse infiltration by elements of malignant lymphoma. The tumor showed a diffuse growth with the monomorphic small-cells size of lymphoid cells around vessels and appendages of skin.
Immunophenotype: We revealed following antigen reactions by immunohistochemistry: CD3+, CD5+, CD56-, CD8- (CD8+ in identity skin cells), TdT-, ALK-, CD20-, CD30-.
Cytogenetics: Cytogenetics has not been done.
Molecular studies: Molecular studies have not been done.
Proposed diagnosis: Primary Cutaneous T-cell prolymphocytic lymphoma IVB (Ann Arbor) and T4 Nx M0 B0 (TNM).
Interesting feature(s) of submitted case: The present case report is interesting because of presentation in the female with primary skin involvement and lymph nodes enlargement in the 6 months after first skin symptoms.

Imprint

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