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BONE MARROW WORKSHOP SESSION 1

ALL and reactive lesions

Chairs: D. Arber, P. Johnston

EAHP18-BMWS-132

B-lymphoblastic leukemia/lymphoma associated with t (8;22)(p11.2;q11.2)/BCR-FGFR1 rearrangement

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Case description: A 51-year-old man with no significant PMH presented with fatigue and nasal congestion and was treated for sinus infection with antibiotics. Within two weeks he returned with worsening palpitations, dyspnea on exertion, and fatigue and was noted to have pallor. He was found to have a high WBC of [57.9] and marked anemia [4.4 g/dl]. Peripheral blood and bone marrow examination were performed.
Biopsy fixation details: The bone marrow core biopsy and the aspirate specimen were fixed in zinc formalin.
Frozen tissue available: No.
Details of microscopic findings: The peripheral blood smear revealed severe normochromic normocytic anemia and leukocytosis with absolute monocytosis, absolute eosinophilia, absolute basophilia, absolute neutrophilia, and absolute lymphocytosis, with left shifted myeloid series.
The bone marrow aspirate smear was aspicular and hemodilute but revealed 7% blasts. The H&E stained biopsy showed markedly hypercellular marrow (>95%) for age. Myeloid precursors were markedly increased and showed full maturation. Erythroid precursors were markedly decreased and the M:E ratio was > 20:1. Megakaryocytes showed occasional cytologic atypia (hyperlobated forms, hypolobated forms, micromegakaryocytes, clustering). Eosinophils were inconspicuous. Scattered and clustered immature mononuclear cells suspicious for blasts accounted for approximately 20% of cellularity.
Immunophenotype: Immunostains performed on the biopsy core revealed that CD34+ TDT+ blasts accounted for 20% of the cellularity. They were also CD19+ CD20+ CD79a+ PAX5+. MPO stained abundant myeloid cells.
Cytogenetics: Conventional cytogenetic and FISH stidies were performed on peripheral blood and revealed the following findings.
Karyotype:
46,XY,t(8;22)(p11.2;q11.2)[20]
FISH:
These were negative for t (9;22)/BCR/ABL1 but positive for an extra copy of BCR (22q11.2) as well as for a FGFR1 (8p11.2) rearrangement in 172/200 cells (86%).
Molecular studies: PCR and DNA sequencing studies were performed.
PCR on peripheral blood:
No BCR/ABL1 fusion transcript or JAK2 V617F mutation was detected.
Sequencing studies on bone marrow aspirate:
Mutation in RUNX1 p.R204* c.610C>T resulting in a premature stop of the coding sequence with allele frequency of 37% was detected.
Proposed diagnosis: Myeloid/lymphoid neoplasm with FGFR1 rearrangement (B-lymphoblastic leukemia/lymphoma associated with t (8;22)(p11.2;q11.2)/BCR-FGFR1 rearrangement).
Interesting feature(s) of submitted case: This B-lymphoblastic leukemia arose in the setting of a myeloid/lymphoid neoplasm with FGFR1 rearrangement. Cases with a t(8;22)(p11.2;q11.2) in which the FGFR1 partner is BCR are rare, but are more likely to show the following somewhat distinctive features, all of which are evident in this case:
1) B-lymphoblastic, rather than T-lymphoblastic, leukemia/lymphomas
2) RUNX1 mutations
3) CML-like hematologic features

EAHP18-BMWS-152

B-lymphoblastic leukemia/lymphoma with MYC and BCL2 rearrangements, arising from follicular lymphoma

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Case description: A 63 year old man initially presented with back and leg pain. Imaging showed multiple osseous lesions and diffuse hypermetabolic lymphadenopathy. Inguinal lymph node biopsy showed follicular lymphoma, grade 3A with BCL2 gene rearrangement. A bone marrow examination showed maturing hematopoiesis with no evidence of lymphoma or acute leukemia. Patient has been treated with one cycle of BR (bendamustine/rituximab) and started feeling unwell with drenching night sweats. LDH markedly increased (up to 4350 IU/L). Peripheral blood had numerous circulating atypical cells with blast-like appearance. A repeat bone marrow biopsy was performed (case submitted).
Biopsy fixation details: Bouin
Frozen tissue available: Yes
Details of microscopic findings: Bone marrow biopsy and aspirate: the cellularity is >90% and consists of a monotonous population of large transformed lymphoid cells. The neoplastic cells have markedly irregular nuclear contours, variably condensed chromatin, one to several nucleoli and moderate amount of basophilic cytoplasm with occasional vacuoles. Some are markedly atypical and anaplastic.
Immunophenotype: The neoplastic cells express dim CD45, CD19, CD20, CD10, TdT and bright lambda immunoglobulin light chain. Tumor cells are negative for CD34.
Cytogenetics: An abnormal complex male karyotype with multiple abnormalities noted. FISH analysis demonstrates IgH-MYC and IgH-BCL2 gene rearrangements.
Molecular studies: Deep VDJ and whole exome sequencing were performed. The TdT+ blastic tumor harbored many somatic hypermutations in the IGH gene, consistent with a germinal center B-cell derivation. Both the follicular lymphoma and the TdT+ blastic tumor shared inactivating mutations in CREBBP and TP53. Two MYC missense mutations in addition to 40 other genetic alterations were identified specifically in the TdT+ blastic tumor.
Proposed diagnosis: B-lymphoblastic leukemia/lymphoma with MYC and BCL2 rearrangements (lymphoblastic transformation of follicular lymphoma).
Interesting feature(s) of submitted case: There are approximately 20 reported cases of follicular lymphoma transformation which results in clinical findings, histology, and immunophenotype reminiscent of B-lymphoblastic leukemia/lymphoma. All cases are characterized by BCL2 and MYC gene rearrangements. The terminology has been controversial and includes lymphoblastic transformation of follicular lymphoma, acute lymphoblastic leukemia, precursor B cell blast crisis, atypical Burkitt lymphoma, and Burkitt-like lymphoma. The updated 2016 WHO classification advises that these cases be classified as “B-lymphoblastic leukemia/lymphoma”.
Many morphologic, immunophenotypic and molecular features of this case appear intermediate between high-grade B-cell lymphoma and B-lymphoblastic leukemia. Some tumor cells have condensed chromatin, while others resemble blasts. Occasional multinucleated/anaplastic tumor cells are seen. There is bright CD20 and bright lambda light chain expression, but dim CD45 and TdT expression. TdT appears expressed in many large anaplastic-appearing cells. Based on deep sequencing, B-lymphoblastic leukemia cells harbored many somatic hypermutations in the IGH gene, consistent with a germinal center B-cell derivation, in contrast to cases of de novo B lymphoblastic leukemia/lymphoma.
Thus, it appears that the B-lymphoblastic leukemia was generated in the bone marrow as a result of clonal expansion from a small divergent subclone preexisting in the follicular lymphoma.

EAHP18-BMWS-258

Hyaline-vascular Castleman changes in the setting of anaemia, thrombocytopenia, organomegaly and marrow fibrosis.

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Case description: 58 year old woman with past history of ITP in 2012 treated with steroids and rituximab who re-presented 4 years later with petichiae and a cough. Her FBC presented bicytopenia (microcytic anaemia and thrombocytopenia) and her blood film showed tear drop poikilocytes. CRP was raised. There was no palpable lymphadenopathy but CT scan showed pleural and pericardial effusions, right middle lobe lung lesion, supraclavicular and mediastinal lymph nodes, anterior mediastinal mass and a bulky spleen. Biopsies of the supra-clavicular and mediastinal lymph nodes showed reactive changes only. During this time she had severe thrombocytopenia, GI bleeding, autoimmune haemolytic anaemia, raised CRP, mild renal impairment and anasarca with a weight gain of over 15kg. She had spontaneous remission of oedema and cough after 3 months but required eventual lung resection to make a diagnosis.
Biopsy fixation details: Lung wedge: 24 hours in formalin
Bone marrow: 24 hours in formalin and then processed to resin
Frozen tissue available: No
Details of microscopic findings: Lung wedge (sample submitted for central review): showed normal lung parenchyma with associated lymphoid tissue which showed many germinal centres with typical hyaline-vascular Castleman changes. Germinal centres were lymphocyte depleted and showed remaining FDC and hyalinisation. B-cells in the mantle zones adopted a classical concentric disposition as in “onion skin” with occasional hyalinised venules entering follicles at 90 degree angles giving ‘lolly-pop’ appearance. Intervening plasma cells are increased but staining for light chains favoured a polytypic infiltrate. HHV8 and LMP1 were negative.
Bone marrow aspirate and trephine (sample submitted for central review): was hypercellular with all three series well represented. There was increased megakaryocytic activity with occasional hyperlobated elements and tendency to form loose clusters. Streaming of haematopoietic cells was patent so that increased reticulin fibrosis was suspected. A Silver stain demonstrated increased grade 1 (MF scoring) reticulin fibrosis with areas of grade 2.
Immunophenotype: Flow cytometry demonstrated blasts with normal phenotype and normal lymphoid subsets without evidence of a clonal B-cell population.
Cytogenetics: No
Molecular studies: JAK2, CALR and MPL were negative
Proposed diagnosis: Idiopathic multicentric Castleman Disease (iMCD) as part of TAFRO syndrome (Thrombocytopenia, Anaemia, Anasarca, Myelofibrosis, Renal impairement and Organomegaly)
Interesting feature(s) of submitted case:
1. Until now most reported cases in patients with Asian/Japanese background. This is one of the first patients with European/Caucasian ethnic background described in the literature and submitted for central review.
2. Very few cases worldwide and pathologist must raise awareness of these syndrome when hyaline-vascular changes are noted.
3. Raising awareness would decrease number of unnecessary tests as well as anxiety for patient initiating prompt treatment with improvement of symptoms
4. Further research must be carried out not only on patients with suspected TAFRO but also on patients with Castleman changes in order to better understand the nature of factors responsible for these changes.
5. Case composed of two different specimens which portrait typical features found in described syndrome. This in combination with presence of other clinical findings typical of TAFRO make this an ideal case for learning.

EAHP18-BMWS-266

5-month-old with acute T-lymphoblastic leukemia (TRA-MYC rearrangement)

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Case description: A previously healthy 5-month old male (ex-36 weeks) presented with two days of fever (peak 39.3°C) and rectal bleeding, and was found to have hepatosplenomegaly, marked leukocytosis, anemia, thrombocytopenia, and tumor lysis syndrome. He was started on rasburicase for hyperuricemia (uric acid 20.2 mg/dL) and cefepime for febrile neutropenia. CBC results at presentation: WBC 521.02 x 10^9/L; HGB 6.4 g/dL; HCT 18.8%; MCV 81.0 fL; PLT 48 x 10^9/L. Manual differential: 9% polys; 15% lymphs; 1.5% monos; 5% eos; 69.5% "other WBCs"; 0.10 nRBC/100 WBC.
Biopsy fixation details: No biopsy taken (aspirate smears only).
Frozen tissue available: None (aspirate smears only).
Details of microscopic findings: The peripheral smear showed numerous large blasts with round to irregular nuclei, prominent nucleoli, finely dispersed chromatin, and moderately abundant pale basophilic cytoplasm with numerous vacuoles.
The bone marrow aspirate showed 1% neutrophils and precursors; 1.5% erythroid precursors; 1% eosinophils; and 96.5% blasts. The blasts were large, and some forms had discrete large, basophilic granules; frequent vacuoles were present, but no Auer rods were seen. MPO cytochemistry showed no definite staining of blasts. Oil Red O stain was negative for lipid in the cytoplasmic vacuoles.
Immunophenotype: A population of abnormal T cells (77% of all cells) expressed CD45, surface CD3 (dim), cytoplasmic CD3, CD2, CD5 (dim), CD7 (dim), CD8 (dim), CD38, CD13 (dim), and were negative for CD4, CD56, CD57, TCRalpha/beta, TCRgamma/delta, CD33, CD34, CD117, HLA-DR, CD10, CD19, TdT, CD1a, CD36, glycophorin, CD123, CD41a, and CD61. MPO flow cytometry showed very weak positivity in blasts, interpreted as non-specific.
Cytogenetics: 46,XY,t(8;14)(q24;q11.2)[20].ish t(8;14)(5'MYC+;3'MYC+)[5]
Molecular studies: No reportable single nucleotide variants or insertions/deletions were detected in genomic DNA by next-generation sequencing (NGS). No reportable fusion transcripts were detected by targeted RNA NGS using Anchored Multiplex PCR.
Proposed diagnosis: T-lymphoblastic leukemia (with TRA-MYC rearrangement)
Interesting feature(s) of submitted case: The T cells lack immunophenotypic features of immaturity (no expression of CD1a, TdT, or CD34) and display some surface CD3 expression, raising the differential diagnosis of a mature peripheral T-cell lymphoma. However, the blastic morphology as well as lack of expression of TCR alpha/beta or TCR gamma/delta favor a precursor T-lymphoblastic neoplasm.
The possibility of a biphenotypic (T/myeloid) leukemia was also considered given the dim positivity for MPO by flow cytometry. However, this was not confirmed by MPO cytochemistry and the lack of expression of other myeloid markers (with exception of very dim CD13) did not support myeloid differentiation.
The TRA/MYC rearrangement is a very rare cytogenetic aberration in T-lymphoblastic leukemia (<2% of cases) and is associated with young age, high tumor burden, and aggressive behavior. This patient achieved excellent clinical response with induction/consolidation chemotherapy and is alive in remission on maintenance chemotherapy five months after diagnosis. In this case, the presence of this recurrent rearrangement provided further support for the diagnosis of T-lymphoblastic leukemia despite the unusual immunophenotype.
Interestingly, the tumor cell cytomorphology resembles Burkitt lymphoma, a B-cell neoplasm that can similarly present as a leukemia, has an analogous rearrangement of MYC with the IGH locus, and (in leukemic form) was previously considered as a 'mature' type of B-acute lymphoblastic leukemia ("L3-ALL").

EAHP18-BMWS-351

Recurrence and lineage switch of a B-cell lymphoblastic leukemia as a myeloblastic leukemia in the skin of a 15 year old boy

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Case description: A fifteen year old boy presented with upper respiratory infection symptoms and progressive fatigue for five days. He was found to be pancytopenic with 68% blasts in peripheral blood, 84% blasts in the subsequent bone marrow aspirate, and 90% blasts in the bone marrow biopsy that were lymphoblastic. He began standard risk induction chemotherapy and had minimal residual disease by flow cytometry in the bone marrow on Day 32. Around the same time, he developed a severe polyneuropathy affecting multiple cranial nerves and all extremities. He was also noted to have a violaceous purpuric rash on the lower extremities and feet that progressed rapidly in the weeks after his day 32 bone marrow. Skin biopsy showed leukemia cutis with a myeloid phenotype . He was then treated with high dose cytarabine and asparaginase and initially responded, but the skin lesions began progressing rapidly 3 weeks later.
Biopsy fixation details: Bone marrow biopsies were fixed in Bouin solution. Skin biopsies were fixed in 10% neutral buffer formalin.
Frozen tissue available: No frozen tissue.
Details of microscopic findings:
Initial diagnositic bone marrow was markedly hypercellular (approximately 100%) and involved with a diffuse population of small to large lymphoblasts with a high N/C ratio, irregular nuclei, many with hand mirror like cytoplasmic projections. A small subset had intracytoplasmic eosinophilic granules and/or fine vacuoles.
Skin biopsy showed a heavy mononuclear cell infiltrate in the deep dermis and panniculus composed of large atypical, hyperchromatic mononuclear cells with scant cytoplasm and scattered mitotic figures.
Immunophenotype:
Bone marrow: The blasts in the diagnostic marrow were positive for: CD34, CD19, CD22, minimal CD10, TdT, CD33, CD38, CD58, CD9, HLA-DR, and partial CD24, CD31; and are negative for CD20 and cytoplasmic myeloperoxidase by flow cytometry**.**
Skin: The blasts in the skin biopsy were immunohistochemically positive for myeloperoxidase, CD43, and lysozyme with a subset weakly positive for CD117; negative for TdT, CD34, CD19, CD79a, and Pax-5. By flow cytometry the blasts in the skin were positive for CD33, CD34 (variable), CD13, and HLA-DR. They lacked CD19 and CD117 expression.
Cytogenetics:
Bone Marrow and peripheral blood FISH was negative for gain of 4, 10, and 17, BCR-ABL fusion, MLL rearrangement, and ERV6-RUNX1 fusion
Peripheral blood karyotype: 46,XY,t(12;17)(p13;q11.2),t(16;17)(p13.3;q11.2)[1]/ 45,sl,-Y,add(9)(p21),add(9)(p13),-20,+mar[17]/ 46,sdl1,+8[2]
Peripheral blood and skin FISH: homozygous deletion of CDKN2A (nuc ish (CDKN2Ax0, CEP 9x2)
Molecular studies:
Immunosequencing bone marrow: IGH clonal rearrangement
Next generation sequencing skin biopsy- a fusion transcript was detected involving TAF15 Exon7 (ENST00000605844.5) and ZNF384 Exon3 (ENST00000355772.8)
Proposed diagnosis:
B lymphoblastic leukemia involving bone marrow and peripheral blood at diagnosis. Subsequent skin biopsy showed lineage switch to acute myeloid leukemia.
Interesting feature(s) of submitted case:
It appears this patient's lymphoblastic leukemia has switched to a myeloid phenotype in the skin. The blasts express myelocytic markers while harboring a TAF15 ZNF384 fusion that is associated with pre-B cell lymphoblastic leukemias. ZNF384-related fusion genes have found to define a subgroup of childhood B-cell lymphoblastic leukemia with characteristic phenotype. These patients were found to have disease at a younger age with early recurrence and overall poorer prognosis. The peripheral blood blasts and skin blasts also have homozygous deletion of CDKN2A, a feature more common in lymphoblastic leukemia.

EAHP18-BMWS-411

TdT positive high-grade B-cell lymphoma with MYC, BCL2 and BCL6 rearrangements

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Case description: A 57 year old lady presented with a right VI cranial nerve palsy. She reported a 2 month history of headaches and 1 stone weight loss in the last month. On examination she had no lymphadenopathy or organomegaly. Hb 104 g/dL, WCC 5.2 x 10^9/L, platelets 62 x 10^9/L. CT showed no solid organ lesion. MRI head showed a 9mm lesion in the left dorsum sellae that could represent a metastatic deposit. However the CSF did not reveal any malignant cells. The bone marrow aspiration and trephine biopsy was the diagnostic test.
Biopsy fixation details: 10% Formalin fixed, decalcified in EDTA.
Frozen tissue available: No
Details of microscopic findings: Bone marrow aspirate: Hypercellular but aparticulate bone marrow aspirate in which normal haemopoiesis is replaced by abnormal cells with an immature appearance.
Bone marrow trephine: markedly hypercellular for the age of the patient (~100%). The marrow spaces are mostly replaced by an immature, monomorphic cell population which amount to >90% of bone marrow cells.
Immunophenotype: Flow cytometry was performed on the bone marrow aspirate and identified 86% atypical B cells (variable weak/strong CD19 positive). These were shown to express strong CD9, CD10, weak CD22, strong CD38, CD43, weak/moderate CD45, strong CD81, variable weak/moderate CD200, strong HLA-DR and were positive for TdT. There was no expression of CD20, CD34 or CD79b and surface light chains were not detected.
Immunohistochemistry showed the tumour cells to be strongly and diffusely immunoreactive with PAX5, BCL2, BCL6, CD10, MUM-1, TdT and MYC. There is loss of CD20 with only a small proportion of positive large tumour cells. CD21, CD30, CD34, CD138 and EBER-ISH were negative; CD3 and CD5 highlighted a minor reactive population of T-cells
Cytogenetics: FISH on the bone marrow aspirate : 85~93% Positive for MYC rearrangement;
90% Positive for the IGH-BCL2 rearrangement, with the presence of an additional fusion signal;
92% Positive for BCL6 rearrangement
Molecular studies: None applicable.
Proposed diagnosis: High-grade B-cell lymphoma with MYC, BCL2 and BCL6 rearrangements
Interesting feature(s) of submitted case: High-grade B-cell lymphomas with MYC, BCL2 and BCL6 rearrangements are a new subclassification in the 2016 WHO Classification of tumours of haematopoietic and lymphoid tissues. This case illustrates this new entity, and highlights the overlap between mature and immature characteristics, in both morphology, histology, immunocytochemistry and immunohistochemistry that may be present in these double and triple "hit" lymphomas. TdT positivity is most commonly seen in immature cells, but is not uncommonly present in high-grade B-cell lymphoma with MYC, BCL2 and/or BCL6 rearrangements. This case also was negative for surface light chains, but positive for MUM-1. The FISH findings of MYC, BCL2 and BCL6 rearrangements in this case are essential to confirm this diagnosis, and this illustrate the importance of these test modalities in the accurate diagnosis of high grade lymphoid neoplasms.

EAHP18-BMWS-272

B Lymphoblastic Lymphoma/Leukemia with t (14; 18) and t(8;22) - ?De Novo or Blastoid Transformation of Follicular Lymphoma

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Case description: 55-year-old male with chief complaint of diffuse rash, dryness and itchiness on his back and abdomen for about a month. Laboratory work up during the visit showed the following -
WBC count 10.9K/uL, Hemoglobin 13.5 g/dL, Platelet count 63K/uL. The WBC differential count included 38% neutrophils, 18% lymphocytes, 20% monocytes, 2% eosinophils and 22% atypical cells with blastoid morphology.
A bone marrow aspiration and biopsy was performed which revealed B lymphoblastic leukemia/lymphoma with 71% blasts.
As a part of staging work up, patient underwent Computerized Tomography examination of abdomen and pelvis which showed retroperitoneal lymphadenopathy
Biopsy fixation details: Bone marrow biopsy and clot sections fixed using 10% neutral buffered formalin for 2 hours. Following fixation they are placed in filtered RDO rapid decalcifier (containing hydrochloric acid) for approximately 15 minutes. After decalcification, specimens are washed thoroughly for 30 minutes in running water after which they are loaded onto processors.
Frozen tissue available: No
Details of microscopic findings: Bone marrow, biopsy:
Overall Cellularity: 80-100%
Sheets of immature appearing lymphoid cells - the immature lymphoid cells have are predominantly medium sized monotonous cells with rounded nuclei, finely dispersed chromatin and small nucleoli. Trilineage hematopoiesis is decreased.
Bone marrow aspirates - markedly decreased trilineage hematopoiesis. Cellularity comprised of predominantly medium-sized blastoid cells with high N/C ratio; nuclear membrane folds or notches and nucleoli in a subset.
Bone marrow aspirate differential count (500-cells) includes 3% myelocytes, 1% metamyelocytes, 3% band forms, 3% neutrophils, 2% monocytes, 17% lymphocytes and 71% blastoid appearing lymphoid cells consistent with lymphoblasts
Immunophenotype: Flow cytometric immunoanalysis of bone marrow aspirate material -
Dim CD45+ cells with low side light scatter in blast gate comprised approximately 18.4% of total events with the following immunoprofile -
Positive for CD19, CD10 (bright), CD20 (heterogeneous), HLA-DR (bright), and dim CD79a.
Negative for CD34, CD5, CD117, CD3, CD7, CD2, CD11b, CD15, CD13, CD16, CD56, CD61, CD235, CD33, CD14, TdT, MPO, kappa and lambda surface immunoglobulin light chains.
Cytogenetics: 47,X,add(Y)(q23),t(8;22)(q24.1;q11.2),t(14;18)(q32;q21),+mar[2]/48,sl,i(1)(q10)[3]/46,XY[15]
Chromosome analysis showed a two cell populations with a complex abnormal karyotype and evidence of clonal evolution in 25% of metaphases examined. Noteworthy abnormalities include a t(8;22) (variant of the t(8;14)) and a t(14;18) resulting in MYC deregulation and a IGH-BCL2 gene rearrangement . These findings are consistent with a double hit lymphoma
Molecular studies: None
Proposed diagnosis: High grade B-cell lymphoma, NOS with t(14;18) and t(8;22), consistent with double-hit lymphoma
Interesting feature(s) of submitted case: The predominance of lymphoblasts, clinical presentation with peripheral blood blasts, extensive marrow involvement and immunoprofile with lack of surface light chains mimic B lymphoblastic leukemia/lymphoma. With leukocytosis as the initial presentation and the presence of blastoid cells in peripheral blood without a previous history of lymphoma, the disease may be misdiagnosed as acute leukemia. Rare cases of de novo B lymphoblastic leukemia/lymphoma can have MYC and BCL2 translocations.

EAHP18-BMWS-287

High grade B-cell lymphoma with blastoid features and MYC/BCL2 “double hit” presenting in the bone marrow concomitant with a biclonal follicular lymphoma.

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Case description: An 87 year old man presented with fatigue and lower extremity edema. CBC showed lymphocytosis, anemia, and thrombocytopenia (WBC 74K/uL - 85% lymphocytes, Hgb 12.7 g/dL and PLT 85K/uL). Bone marrow biopsy was performed, which showed a high grade B-cell lymphoma with blastoid features and a component of follicular lymphoma (FL). Peripheral blood flow cytometry (FC) and smear indicated involvement by FL. SPEP and UPEP with IFE detected trace IgG kappa paraprotein and free lambda light chains. A subsequent CT scan showed generalized lymphadenopathy and moderate splenomegaly (12 cm). Modified R-CHOP chemotherapy was started, but the patient developed renal failure and uremia and died due to hemorrhagic shock, 2 weeks after presentation.
Biopsy fixation details: B-plus
Frozen tissue available: No
Details of microscopic findings: The bone marrow biopsy was markedly hypercellular (90%) and showed multifocal infiltrates of intermediate to large lymphocytes with blastoid features (fine chromatin, prominent nucleoli and scant cytoplasm) and interspersed aggregates of small to medium-sized lymphocytes with centrocytic morphology. The peripheral blood smear showed numerous lymphocytes with bi-lobed or cleaved nuclei, fine chromatin, and scant cytoplasm. The aspirate showed blastoid appearing cells, some with cytoplasmic vacuoles.
Immunophenotype: By IHC, the large lymphocytes expressed CD20, PAX5, CD79a, CD10, HGAL, MUM1, FOXP1, BCL2, TdT(subset), and c-MYC (90%). They were negative for CD5, BCL6, LMO2, SOX11, cyclinD1, and P53. The small lymphocytes showed partial BCL6 expression, but they were MUM1 and c-MYC negative.
FC of the bone marrow aspirate detected multiple B-cell populations: The CD45+, low SSC gate (46% of events) showed CD10+ kappa (72%) and lambda (12%) restricted B-cells that were small (by FSC) and had the following phenotype: CD19(dim)+, CD79a+, CD20+, CD23+/-, CD38+, HLA-DR+, FMC7+, CD25-/+, CD5-, CD103-, CD43-, CD11c-, CD34-, sIgM- and sIgD-. The CD45+, high SSC gate (45% of events) showed kappa restricted B-cells that were large in size (by FSC) and had the following phenotype: CD19+, CD79a(dim)+, CD20+/-, CD10+, CD38+, HLA-DR+, FMC7+/-, CD25-, CD5-, CD23-, CD30-, CD103-, CD43-, CD11c-, CD34-, sIgM- and sIgD-.
FC of the peripheral blood showed kappa (54% of events) and lambda (11%) restricted CD10+ B-cells with the same phenotype as the small lymphocytes in the marrow. No large lymphocytes were identified.
Cytogenetics: G-band karyotype of the bone marrow aspirate showed:
47,XY,t(1;9)(p12;p21),+i(1)(q10),t(3;10)(p13;q26),t(8;14)(q24;q32),del(9)(p21),t(14;18)(q32;q21)[5]/49,idem,+X,-der(14)t(14;18),+14,+21[15]. FISH analysis showed IGH, BCL2, and MYC rearrangements in 97%, 80%, and 73.5% of cells, respectively. BCL6 break-apart probe showed no rearrangement. The LSI 9q21/CEP 9 probe showed 9q21 (CDKN2A) heterozygous deletion in 86% of cells.
Karyotype of the peripheral blood showed: 46,XY,del(1)(p31),+i(1)(q10),del(3)(p13),-9,add(14)(q32),+mar. FISH analysis showed IGH and BCL2 rearrangements; no MYC or BCL6 rearrangements were detected.
Molecular studies: PCR for IGH gene rearrangement showed clonal products.
Proposed diagnosis: High grade B-cell lymphoma with blastoid features and MYC/BCL2 “double hit” (DH) in the marrow in a patient with leukemic-phase biclonal follicular lymphoma.
Interesting feature(s) of submitted case: This is an unusual case of a biclonal FL with a seemingly rapid onset, in leukemic phase, associated with biclonal paraproteinemia and a high grade DH lymphoma detected in the marrow at presentation. TdT expression by a subset of lymphoma cells suggested lymphoblastic transformation.

EAHP18-BMWS-361

High-grade B-cell lymphoma with MYC rearrangement and immature markers

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Case description: A 67-year old female on treatment for hypertension, otherwise healthy, experienced fatigue for some months. A bone marrow examination was performed due to anemia and thrombocytopenia. HB: 87g/L, WBC: 12.1x10^9/L, PLT: 18x10^9/L, S-LDH: 90. On physical and radiological examination neither lymph node enlargements nor hepatosplenomegaly was observed. Peripheral blood was sent for flow cytometry (referral hospital).
Biopsy fixation details: Bone marrow biopsy fixed in buffered 4% formalin
Frozen tissue available: No frozen tissue available.
Details of microscopic findings: Bone marrow examination: Biopsy 23 mm with hypercellularity and excess of blasts. Normal hematopoiesis was reduced. Blasts were medium to large in size with finely dispersed chromatin and contained one to several nucleoli.
Immunophenotype: Flow cytometry of blood: Blast cells 20-30% CD45dim, CD19+, icCD79+, icCD22+, CD20dim/neg, CD10dim, TdT+, CD38+, IgM and surface Igkappa+. Negative for: CD34, CD13, CD33, CD15, CD117, MPO, cytCD3, CD4, CD2, CD5, CD8, CD7.
Immunohistochemistry: Blasts were positive for CD79a, partially CD20, CD10, BCL-2, TdT, MYC, MUM1, FOXP1 and kappa. Negative markers: CD34, BCL-6, lambda, p53, CD5, CD23, CD30
In situ hybridisation for EBER: negative
Cytogenetics: Hypotetraploidy with 80-83 chromosomes with t(8;14); IGH-MYC
80~83<4->inc[7]/46,XX[13]ish t(8;14)(q24;32)(CEP8+, MYC+,IGH+;IGH+,MYC+)[5/8].nuc ish(ABL1x2,BCRx3-4)[62/244]/(MLLx3)[70/227]
Molecular studies: Not performed
Proposed diagnosis: High-grade B-cell lymphoma with MYC rearrangement and immature markers.
Interesting feature(s) of submitted case: ·Difficulties in the differential diagnosis and dilemma in classification: High-grade B-cell lymphoma with MYC rearrangement and immature markers **or** B-ALL with MYC rearrangement and surface Ig kappa light chain restriction?

EAHP18-BMWS-443

Marrow presentation of a high-grade B-cell lymphoma with rearrangements of MYC and BCL6, BCL2 amplification and an immature phenotype

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Case description:
A 62 year old male patient presented with pleural effusion and a significant leucocytosis (19,230 cells/mm³). The latter contained 65.5% monotypic CD5+ atypical B-cells.
A PET scan showed a diffuse hyperintense signal in the bone marrow, spleen in association with the pleural effusion. A bone marrow biopsy was performed which demonstrated a high-grade B cell lymphoma (HGBL) with rearrangements of MYC and BCL2 and/or BCL6 and features suggestive of immaturity.
The patient was treated by DA-EPOCH-R and intrathecal methotrexate with partial remission. He relapsed and died 11 months after his diagnosis.
Biopsy fixation details: 10% neutral buffered formalin followed by decalcification with a 10% formic acid/5% formaldehyde solution.
Frozen tissue available: No
Details of microscopic findings:
A hypercellular bone marrow (over 90% cellularity) showing an extensive infiltrate (approximately 80%) of small to medium-sized rounded cells with “blastoïd” morphology. The infiltrating cells showed slightly irregular nuclei and minimal cytoplasm; occasional larger nucleolated forms were also present.
Immunophenotype:
By flow cytometry the abnormal cells were CD45+, HLA-DR bright+, CD19+, CD22+, CD20+, Kappa+, CD3-, CD5+, CD10- CD11c-.
Parafin section immunophenotype: CD34-, CD117-, MPO-, CD13-, CD33-, CD20+, CD79a+, CD19+, Pax5+, CD3-, CD5+, CD10 focally+, Bcl6 weakly+, Bcl2+, and c-myc+. TdT was expressed on 50-60% of the infiltrating cells and a scattered subpopulation (5%) was EBER positive. CyclinD1 and Sox11 were negative. Ki67 showed a proliferation fraction of 60-70%.
Cytogenetics:
-Complex Karyotype:
51,XY,+1,add(1)(p34),add(2)(q11),der(3)t(?2;3)(q?;q27),add(4)(q3?1),+7,t(8;14)(q24;q32),t(11;12)(q23;p13),del(13)(q?14),+3mar[12+8c].
-FISH: IGH-MYC rearrangement [90%], BCL6 rearrangement [78%] and BCL2 amplification [98%].
Molecular studies: B cell clonality (monoclonal FR1 and FR3)
Proposed diagnosis: High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with expression of TdT and CD5 and focal EBV positivity
Interesting feature(s) of submitted case: Unusual/aberrant expression of TdT and CD5 and focal EBV staining.

EAHP18-BMWS-108

SF3B1 mutated B-lymphoblastic leukemia/lymphoma arising from myelodysplastic syndrome with ring sideroblasts

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Case description: The patient is an 85 year old man who presented with fatigue. He had a history of myelodysplastic syndrome diagnosed 6 years earlier when he was found to have anemia. Bone marrow examination at that time showed hypercellular bone marrow with dyserythropoiesis and 70% ring sideroblasts. There was no increase in blasts. He was maintained on lenolidamide therapy without transfusions. At the time of presentation, a CBC showed a hemoglobin of 7.5 g/dL, Hct 23.9%, MCV 99.7 fL, platelets 277 x 10^3/uL, and WBC 1.7 x10^3/ul with 8% circulating blasts. Peripheral blood flow cytometry and a bone marrow examination were performed.
Biopsy fixation details: The Biopsy was fixed in bouins.
Frozen tissue available: Yes.
Details of microscopic findings: The bone marrow biopsy was hypercellular (95%) with a diffuse proliferation of blasts comprising 70% of marrow cellularity. Trilineage hematopoiesis was decreased with rare hypolobated megakaryocytes. A small lymphoid aggregate was noted. The bone marrow aspirate showed increased blasts, hypogranular, dysplastic neutrophils, and megaloblastoid erythroid precursors. Iron studies showed 85% ring sideroblasts. The blasts were negative for MPO and NSE by cytochemistry.
Immunophenotype: By flow cytometry, the blasts expressed CD10, CD19 (bright), TdT, cCD79a, CD81, and showed dim expression of CD34, CD22, CD20, and CD99. They lacked expression of CD3, surface light chain, CD33, CD13, and CD117.
Cytogenetics: Normal male karyotype. FISH for BCR-ABL1 was negative.
Molecular studies: Targeted next generation sequencing panel showed pathogenic mutations in SF3B1 (H662Q, 45% VAF) and IDH2 (R140Q, 49%). A variant of unknown significance was detected in DNMT3A (D531N, 41% VAF).
Proposed diagnosis: B lymphoblastic leukemia/lymphoma.
Interesting feature(s) of submitted case: This case represents B-lymphoblastic leukemia/lymphoma arising from an antecedent myelodysplastic syndrome. The SF3B1 mutation is strongly associated with myelodysplastic syndrome with ring sideroblasts and has not been described in B-ALL. This mutation was detected at a high variant allele frequency at the time of B-ALL diagnosis, suggesting that both the neoplastic B lymphoblasts and the dysplastic myeloid cells arose from the same clone. Transformation of MDS to lymphoblastic leukemia is believed to be a rare event with only sporadic case reports published in the literature. A recent study demonstrated that SF3B1 mutation originates in hematolymphoid stem cells with the potential to differentiate into myeloid and pro-B-cells. Although myeloid leukemias arising from MDS have a poor prognosis, this patient achieved remission with rituxan, vincristine and prednisone and is currently doing well on rituxan maintance.

EAHP18-BMWS-109

Importance of identifying Early T-cell precursor lymphoblastic leukaemia/lymphoma in the management of patients with T-lymphoblastic leukaemia/lymphoma

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Case description: A 22 year-old female patient presents to A&E department with 3 week history of fatigue, night sweats, lethargy and easy bruising. She was 9 weeks pregnant. A full blood count performed at that point showed WBC 45.2 $x10^9$/L, Hb 124 g/L, Platelets 42 $x10^9$/L. Peripheral blood morphologic examination showed small blast cells. The patient was then referred to a tertiary centre for further assessment.
Biopsy fixation details: 10% formalin 24 hours then processed into resin
Frozen tissue available: No frozen tissue available
RNA available
Details of microscopic findings: Peripheral blood: 90% small blasts with high N:C ratio and occasional vacuoles and many smear cells.
Bone marrow aspirate/trephine: maximally cellular with 90% small blasts and many smear cells. Normal haematopoiesis was very reduced.
Immunophenotype: Immunophenotype:
80% blast cells had the following phenotype: CD45dim+/CD34-/mCD3-/iCD3+/CD1a-/CD2+/CD4-/CD5-/CD7+/CD8-/TCRab-/TCRgd-/CD117+/CD15-/CD13+/CD33-/HAL-DR-/CD14-/CD56-/CD19-/CD10+/CD20-/Tdt-/iCD79a-/iMPO-

Immunehistochemistry: CD99+/CD1a-/CD3+weak/CD5-/CD4-/CD8-/CD7+/CD34-/CD117+weak/Tdt-
Cytogenetics: 46, XX [20]
Molecular studies: DNMT3A mutation
Proposed diagnosis: Early T-cell precursor lymphoblastic luekemia/lymphoma
Interesting feature(s) of submitted case: Characteristic T-cell phenotype (absence CD1a, CD8 and CD5)
Characteristic co-expression of myeloid markers (CD117, CD13)
Presence of mutations characteristic of myeloid disorders (MDS/AML)
Raise awareness of importance of identifying these cases for appropriate therapeutic decisions (benefit from intensive chemotherapy and transplant if suitability).

EAHP18-BMWS-120

B-Acute lymphoblastic leukemia with early switch to monocyte lineage.

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Case description: Previously healthy 10 years old girl who presented with four weeks of fever and headache. Complete blood picture showed WBC 13.4 x 10^9/L, Hb 86 g/L , plt. 36 x10^9/L. Peripheral blood smear showed 80% blasts.
Biopsy fixation details: Bone marrow aspirate and decalcified biopsy with Agartz (fixed in 4% formaldehyde)
Frozen tissue available: Yes
Details of microscopic findings: Hypercellular with 100% cellularity. The bone marrow was dominated by diffuse infiltration of blast cells. Few megakaryocytes. Remarkably reduced erythropoiesis and mature granulopoiesis. Cellular smears dominated by blast cells (95%).
Immunophenotype: Blast cell population (90%) positive for CD45, CD34, CD19, CD22-/dim, CD58, TDT, CD38, CD123, CD33-/dim, CD2-/+ and negative for CD10, CD66c, CD20, MPO and other T-cell markers.
Cytogenetics: 47 chromosomes with extra X chromosome, del (9p).
Molecular studies: MRD screen was performed to find ASO (allele specific ligonucleotides) markers for the patient in order to follow up using RQ-PCR. Primers were design for every clone and then tested in order to find good quantitative range and sensitivity range for MRD
Proposed diagnosis: B-Acute lymphoblastic leukemia with early switch to monocyte lineage.

Interesting feature(s) of submitted case: This child presented with a B-acute lymphoblastic leukemia. On day 15 bone marrow examination showed morphological remission but with a remarkable increase of monocytes while flow cytometry showed a 40% pathological immature cell population with B-cell and monocyte markers (CD19dim,CD34,CD2dim,CD33+, CD13dim,CD123dim/+,CD10-) which was not identical to the leukemic cell population at time of diagnosis. Molecular analysis showed > 25% leukemic popualtion. IHC showed leukemic infiltration positive for CD19 and CD14.

EAHP18-BMWS-125

B-lymphoblastic leukemia, BCR-ABL1-like, with unusual cytoplasmic granules and CRLF2/IGH rearrangement

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Case description: The patient is an 88-year-old female who had previously been in good health. She presented to the emergency room with fatigue, some osteoarthritis-like pain, shortness of breath and dyspnea on exertion for the last month. She noted that her ankles had started to swell, became heavy and red, especially the right leg. An ultrasound revealed a deep venous thrombosis and superficial venous thrombosis in the right leg. She was started on Apixaban anticoagulant and was discharged to follow up with her primary physician. At follow-up several days later, a complete blood cell count showed Hgb 9.7 g/dL; RBC 3.05 x10(12)/L; MCV 98.7 fL; RDW 19.0%; WBC 19.5 x10(9)/L; PLT 115 x10(9)/L. White blood cell differential %: neutrophils 3; lymphocytes 10; blasts 87.The patient died of disease 4 months later.
Biopsy fixation details: B5 fixation/decalcification
Frozen tissue available: NA
Details of microscopic findings: Peripheral blood smear: Circulating blasts, small to medium, with round nuclear contours, smooth chromatin, inconspicuous nucleoli and a scant rim of cytoplasm often containing large, chunky, lightly axurophilic globular inclusions/granules. In occasional cells, the granules/inclusions mimic Chediak-Higashi inclusions.
Bone marrow aspirate: Prominent blastic population with cytologic features similar to those seen in the peripheral blood. In addition, frequent cytoplasmic blebbing is noted in the blasts, which in addition to the cytoplasmic granulation/inclusions, may be misleading for a myeloid process. Background trilineage hematopoiesis is markedly decreased.
Bone marrow core biopsy: Markedly hypercellular bone marrow with near complete effacement by blasts. Scattered residual megakaryocytes with unremarkable morphology are noted. On high power examination, the blasts are distinctive with some showing small forms with indistinct nucleoli while others are large with open chromatin and a single nucleolus.
Immunophenotype: Cytochemical stain, myeloperoxidase, peripheral blood: Negative in the blast population.
Flow cytometric immunophenotyping on the peripheral blood revealed a B-lymphoblast population with the following immunophenotypic characteristics:
Express: CD34, CD19 (dim), CD10 (bright), CD13 (partial dim), CD33 (partial dim), HLA-DR, TdT, cCD22 (partial), cCD79a, CD66c
Do not express: CD45, CD117, CD3, CD20, MPO, CD38
Cytogenetics: Chromosomes: Normal female karyotype; 46,XX[20]
FISH: Abnormal. CRLF2/IGH rearrangement in 88.8% of nuclei.
Molecular studies: JAK2 gene sequencing pending
Proposed diagnosis: B-lymphoblastic leukemia, BCR-ABL1-like, (CRLF2/IGH)
Interesting feature(s) of submitted case: There are several interesting features of this case.
1) B-lymphoblastic leukemia with unusual morphology: cytoplasmic granules/globules, occasionally large and simulating Chediak-Higashi granules, potentially initially mimicking acute myeloid leukemia.
2) B-lymphoblastic leukemia, BCR-ABL1-like, (Ph-like) is common in adults (20-25%). This case harbors the CRLF2/IGH which is one of the more common genetic findings. Importantly this genetic alteration may be cytogenetically cryptic. Concomitant JAK2/JAK1 mutations are seen in approximately 50% of CRLF2-rearranged cases.
3) Karyoptyically normal B-lymphoblastic leukemia. This case highlights the absolute necessity for certain FISH/molecular testing to identify and properly diagnose B-LL.
4) B-lymphoblastic leukemia; BCR-ABL1 like has a poor prognosis as exemplified in this case.
5) The identification and diagnosis of B-lymphoblastic leukemia, BCR-ABL1-like, may allow for treatment with tyrosine kinase inhibitors.

EAHP18-BMWS-139

Early T-cell Precursor Lymphoblastic Leukemia with CD56 Expression

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Case description: A 7-year-old male presented to the emergency room after a 2 week history of intermittent fever, abnormal gait, and coordination difficulties. He was found to have pancytopenia with WBC 0.1, Hgb 7.7, Plt 27,000, hyponatremia, and hepatitis (AST 853 ,ALT 467). Imaging was negative. The patient was seen by pediatric oncology and a bone marrow biopsy was performed. His CFS was negative for leukemia.
Biopsy fixation details: B+ fixative and decalcification with Decal STAT.
Frozen tissue available: None
Details of microscopic findings: Examination of the aspirate smears reveals 98% small lymphoid cells with scant cytoplasm consistent with lymphoblasts. Background hematopiesis was virtually absent. The bone marrow biopsy was hypocellular for age (30%) with stromal damage and marked reduction in normal marrow elements. The majority of the cells were small lymphoblasts.
Immunophenotype: By flow cytometry, the blasts expressed CD7, CD33, CD34, CD38, CD45, dim TdT, and CD56. They were negative for CD2, CD3 (surface & cytoplasmic), CD4, CD5, CD8, myeloperoxidase, CD19, CD20, CD10, and CD1a. By immunohistochemistry, the blasts expressed CD3, CD7, CD56, CD33, and TdT. They were negative for CD1a, myeloperoxidase, CD2, CD4, CD5, CD8, CD10, CD19, and CD20.
Cytogenetics: 46, XY. FISH for BCR-ABL was negative.
Molecular studies: None.
Proposed diagnosis: Early T-cell lymphoblastic leukemia with expression of CD56
Interesting feature(s) of submitted case: CD56 expression in T-lymphoblastic leukemia is associated with a lower 5-year survival and disease free survival and an independent risk factor for CNS involvement in adults. This patient also has an Early T-cell lymphoblastic leukemia (ETP) immunophenotype (CD33+, CD34+, CD8 -, CD5 -, CD1a) which is associated with worse prognosis. Despite these worrisome immunophenotypic findings, the patient achieved remission at day 29 of induction (MRD negative) and MRD was negative at consolidation. The available literature of CD56 expression as an independent prognostic factor is primarily in the adult population. While there are studies of ETP in the pediatric population, the role of CD56 alone is less clear in children.

EAHP18-BMWS-157

B-Lymphoblastic leukemia presenting after lenalidomide therapy for myeloma

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Case description: An 85 year-old woman with history of IgG kappa plasma cell myeloma diagnosed in 2014 treated with lenalidomide and dexamethasone presented to another hospital with fever 3 weeks status post a hip replacement. She was found to be neutropenic with Klebsiella pneumonia bacteruria and Clostridium difficile colitis for which she was treated with ciprofloxacin and metronidazole. However her neutrophil count continued to drop despite filgrastim therapy, and she was transferred to our institution. A bone marrow biopsy was performed. At the time of the biopsy she was pancytopenic (WBC $1.23x10^9$/L; HGB 8.3 g/dL; PLT $41x10^9$/L). There was no evidence of disease in the cerebrospinal fluid. She was started on the modified Larson regimen (cyclophosphamide, daunorubicin, vincristine, prednisone, L-asparaginase) with intrathecal methotrexate. A day 30 bone marrow was negative for persistent disease.
Biopsy fixation details: The trephine biopsy was fixed in zinc formalin and decalcified with hydrochloric acid/EDTA. The clot section was fixed in zinc formalin.
Frozen tissue available: None
Details of microscopic findings: The bone marrow aspirate was aspicular and hemodiluted, however the touch imprints were notable for many large atypical cells with high nuclear: cytoplasmic ratios, scant to moderate agranular cytoplasm, occasionally with vacuoles, irregular nuclear contours, and evenly dispersed chromatin. The trephine biopsy showed effacement of normal bone marrow architecture and a diffuse infiltrate of large atypical cells. These often had irregular or convoluted nuclear contours, relatively finely dispersed chromatin, and occasional prominent nucleoli.
Immunophenotype: By flow cytometry the atypical cells were positive for CD10, CD19, CD20, (bright), CD22, CD38, CD45, and HLADR. They were negative for CD2, CD3, CD4, CD5, CD7, CD8, CD11b, CD13, CD14, CD16, CD33, CD34, CD56, CD64, CD65, CD117, and kappa and lambda surface immunoglobulin light chains.
Immunohistochemistry was also performed. The atypical cells were positive for CD10, CD20, BCL2, TDT, but were negative for CD3, CD7, CD30, CD34, cyclin D1, BCL6, and MUM1. EBER chromogenic in situ hybridization was also negative. MYC was positive in approximately 30% of malignant cells. CD138 showed less than 5% plasma cells, which were polytypic by kappa and lambda staining.
Cytogenetics: 46,XX [20]
Molecular studies: FISH studies for KMT2A rearrangement and BCR/ABL1 were negative
Proposed diagnosis: B-lymphoblastic leukemia, not otherwise specified
Interesting feature(s) of submitted case: This is a case of a patient with a 3 year history of myeloma treated with lenalidomide who developed pancytopenia which was due not to persistent/recurrent myeloma, but to the development of B-lymphoblastic leukemia. Acute lymphoblastic leukemia has been reported in patients receiving lenalidomide for both myelodysplastic syndromes and myeloma, in clinical trials and as case reports. Diagnosis in this case was complicated by a hemodiluted aspirate and somewhat abnormal blast immunophenotype (bright CD20, also lacking CD34). Some authors have posited that increased risk is associated with duration of lenalidomide therapy; we are likely to see increased occurrences of these cases as more patients are treated with this drug. **EAHP 2018 Bone Marrow Workshop Case Submission**

EAHP18-BMWS-185

Lymphoblastic transformation of follicular lymphoma

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Case description: A 51-year-old man with a history of treated low-grade follicular lymphoma (fludarabine, cyclophosphamide, and rituximab completed 9 months prior) presented with bleeding gums, headache, flank pain, and anemia (Hb 10.6 g/dL), thrombocytopenia (platelets 121 K/uL) and WBC of 8.5 K/uL with 49% blasts. Imaging detected extensive hypermetabolic disease involving lymph nodes (cervical, thoracic, abdominal, pelvic), spleen, bilateral kidneys, and bones. Bone marrow and submandibular lymph node biopsies were obtained. A previous retroperitoneal lymph node needle biopsy performed 16 months prior was reviewed.
Biopsy fixation details: Formalin-fixed/paraffin-embedded (bone marrow biopsy following decalcification)
Frozen tissue available: None
Details of microscopic findings:
Bone marrow: Hypercellular (90-100%,) with numerous intermediate-size blasts with round to oblong nuclear contours, fine chromatin, prominent nucleoli, and scant agranular cytoplasm.
Right submandibular lymph node: Effaced by sheets of small to intermediate-size neoplastic cells with fine chromatin, one or more nucleoli, and scant cytoplasm. No features of low-grade follicular lymphoma were present.
Retroperitoneal lymph node (retrospective review): Sclerotic tissue with a vaguely nodular infiltrate of small centrocytes with irregular nuclear contours and few centroblasts (<15/HPF).
Immunophenotype:
Bone marrow and submandibular lymph node:
- Flow cytometry
Positive for:
CD19
CD20 (dim minor subset)
CD10
CD38
TdT
Kappa (dim)
CD45 (dim)
Negative for:
CD34
CD117
CD22
Myeloid antigens
- Immunohistochemistry
Positive for:
PAX5
CD20 (subset)
BCL6
BCL2
MYC
TdT
Retroperitoneal lymph node:
- Flow cytometry
Positive for:
CD19
CD20
CD10
Kappa
- Immunohistochemistry
Positive for:
CD20
CD10

BCL2
CD23 (follicles)
Cytogenetics:
Karyotype (blood):
46,XY,del(5)(q15q22),t(8;9)(q24;p13),del(14)(q24q32),t(14;18)(q32;q21)[20]
FISH (blood): Positive for MYC gene rearrangement.
Cytogenomic array (blood):
- Loss of 18.8 Mb at 5q21.3q23.2;
- Heterogenous loss of 1.5 Mb at 9p21.3 involving homozygous loss of CDKN2A/CDKN2B; and
- Loss of 36.6 Mb at 14q24.1q32.33.
FISH (retroperitoneal lymph node biopsy, per report): Positive for IGH/BCL2 translocation
Molecular studies: B cell clonality studies detected identical IGH rearrangements within the retroperitoneal (low-grade follicular lymphoma) and right submandibular (lymphoblastic lesion) lymph nodes.
Proposed diagnosis: Lymphoblastic transformation of follicular lymphoma
Interesting feature(s) of submitted case: The immunophenotypic features, including surface kappa light chain expression, showed some parallels with the previously diagnosed follicular lymphoma. However, the morphologic features and TdT positivity indicated a lymphoblastic proliferation. The differential diagnostic considerations included de novo B-lymphoblastic leukemia and lymphoblastic transformation of follicular lymphoma. Surface light chain positivity has been reported rarely in B-lymphoblastic leukemia. On the other hand, previously reported cases of lymphoblastic transformation of follicular lymphoma have shown characteristic loss of surface light chain to varying degrees, loss of BCL6, and preserved expression of PAX5, BCL2, and CD10, as well as MYC gene rearrangement. All of these features (except loss of BCL6) were demonstrated in the current case. It has been suggested that because the clinicopathologic findings in lymphoblastic transformation of follicular lymphoma are unique, including poor prognosis (survival of approximately 4 months), such cases should not be classified as either B-ALL or high-grade B cell lymphoma with MYC and BCL2 rearrangements.

EAHP18-BMWS-200

Bone marrow infiltration by a dim CD79a and PAX5+ acute leukaemia with RUNX1 mutation

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Case description: A bone marrow biopsy of a 83-years old male patient was taken due to massive leucocytosis and blasts of 10% in the peripheral blood. The biopsy showed infiltrates of an acute leukaemia with high proliferative activity being weakly positive for CD79a, partially and dim positive for PAX5 and positive for TdT and CD34. T-cell markers remained negative, as well as CD10, CD19, CD20, CD38 and myeloperoxidase (MPOX). Therefore, an acute lymphoblastic B-cell leukaemia (B-ALL) was considered.
A simultaneously performed flow-cytometry favoured an undifferentiated, MPOX-negative acute myelogenous leukaemia (AML). Due to that discrepancy, supplemental molecular diagnostics were initialised. A customized lymphoma NGS panel could not detect lymphoma-typical mutations. Analysis with a myeloid NGS panel rendered two mutations in the transcription factor RUNX1 (G165fs and E86fs), furthermore, mutation of the splicing factor SRSF2 and a splice site BCR 3' mutation were found to be mutated. Cytogenetics showed a tetrasomy of chromosome 13.
In summary, a B-ALL was suspected morphologically, standing in contradistinction to the results of the flow-cytometry and cytogenetics, which all favoured an AML. Molecular findings were not fully conclusive since RUNX1 and BCR mutations can be associated with B-ALL, whereas SRSF2 mutations are almost exclusively found in myeloid disorders. Hence, the integrative diagnosis was rendered as an AML, assuming that the observed RUNX1 mutations might have similar effects on the expression of CD79a and PAX5 like the RUNX1-RUNX1T1 fusion transcript in t(8;21) AML. Therefore, the positivity for CD79a and PAX5 was interpreted as aberrant and not lineage-specific.
Biopsy fixation details: formalin-fixed paraffin embedded
Frozen tissue available: none
Details of microscopic findings: Representative bone marrow biopsy with diffuse infiltrates of leukemic blasts and subtotal extrusion of the haematopoiesis.
Immunophenotype:
positive: CD34, CD44, BCL6, TdT, C-MYC, BCL2, partially dim for CD79a and PAX5
negative: CD2, CD3, CD10,CD11C, CD14, CD19, CD20, CD38, MPOX
ki67: 80%
Cytogenetics: 48, XY, +13, +13
Molecular studies:
- Customized lymphoma panel (68 analysed genes): no mutations found
- Customized myeloid panel (39 analysed genes):
RUNX1: G165fs (46%)
RUNX1: E86fs (48%)
SRSF2: P95L (49%)
BCR 3': splice site mutation (48 %)
Proposed diagnosis: Diffuse bone marrow infiltration by an acute leukaemia, immunophenotypically lymphoblastic B-ALL, integratively AML with minimal differentiation
Interesting feature(s) of submitted case: The case shows a misleading discrepancy between morphology and immunohistochemistry on the one hand and the molecular and cytogenetic results on the other. The dim positivity of CD79a and PAX5 indicates a B-cell differentiation and is suggestive of a B-ALL. However, the molecular results, especially the identified SRSF2 (and RUNX1) mutations and the cytogenetics challenge this diagnosis. Assuming that the RUNX1 mutation might have had analogous impact on the CD79a and PAX5 expression like the RUNX1-RUNX1T1 fusion transcript (Tiacci et al. Cancer Res 2004) we integratively interpreted the positivity for CD79a and PAX5 as most probably aberrant and not lineage-specific. This case illustrates a not yet described potential pitfall in the differential diagnosis of RUNX1 mutant acute leukaemia that is not considered in the new WHO-classification.

EAHP18-BMWS-235

Acute lymphoblastic leukemia of B-cell lineage (B-ALL) in a patient with history of follicular lymphoma

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Case description: A 42 year old patient in treatment with Rituximab for a follicular lymphoma (grade 2, Stage IV, diagnosed 7 months ago) presented himself in a secondary hospital with new onset of tiredness. Blood work showed pancytopenia necessitating thrombocyte transfusion. Bone marrow aspiration was performed and only a biopsy could be obtained (dry tap). The patient was then referred to our hospital for treatment. Patient has a history of beta-thalassemia minor and traumatic pneumothorax in 1980. The biopsy from the previously diagnosed follicular lymphoma was reviewed and the diagnosis was confirmed (material not submitted).
Biopsy fixation details: Fixed in 10% neutral buffered formalin, decalcified in EDTA.
Frozen tissue available: No.
Details of microscopic findings: Hypercellular bone marrow biopsy with diffuse infiltrates of small cells with oval nuclei with finely granular chromatin. Strongly reduced hematopoiesis can be seen in the background. Slightly increased reticulin network.
Immunophenotype: B-ALL: Expression of TdT, CD79a, PAX5, CD10, Myc and BCL2. No detectable expression of CD34, MPO, CD117, CD20, CD3, CD5, Cyclin-D1, CD21 and CD23.
Cytogenetics: Array CGH: 1p36.11 deletion and 9p deletion detected. High hyperdiploidy, hypodiploidy, IKZF1 intragenic deletion, iAmp(21), ERG intragenic deletion and CRLF2-P2RY8 fusion not detected.
FISH: BCL2 and MYC rearrangements detected (both with break apart probes). BCR-ABL1 fusion not detected (dual fusion probe), KMT2A and TCF3 rearrangement not detected (both break apart probes).
Molecular studies: B-ALL
PCR for t(14;18) translocation: 211bp amplification product (MBR/JH6).
IGH genotyping: monoclonal rearrangement, productive (IgHV3-13*01, IgHD6-6*01, IgHJ4*02)
IGH mutational status: <2 %
NRAS (exon 2): p.G13D mutation
Follicular lymphoma
PCR for t(14;18) translocation: 211bp amplification product (MBR/JH6).
IGH genotyping: monoclonal rearrangement, productive (IgHV3-11*06, IgHD6-6*01, IgHJ4*02)
IGH mutational status: 11,7 %
NRAS (exon 2): no mutation detected
Proposed diagnosis: B-lymphoblastic leukemia, not otherwise specified (B-ALL, NOS) transformed from a follicular lymphoma grade 2.
Interesting feature(s) of submitted case: This is a rare case of B-lymphoblastic leukemia arising from a follicular lymphoma. The immunophenotype of this B-ALL is mostly consistent with a classical presentation but shows expression of Myc protein in >90% of neoplastic cells. Transformation of follicular lymphoma to a precursor lymphoid neoplasm is a rare event only seldom described in the literature. In line with previous studies, our case shows in addition to the common t(14;18) translocation a MYC rearrangement plus an activating NRAS mutation in the B-ALL. IGH PCR followed by fragment analysis of both probes shows monoclonal rearrangements, but with differently sized amplification products. However, IGH genotyping identifies in both neoplasms an identical D-J rearrangement including the N-nucleotides, but different V-element usage. The B-ALL carries a minimally mutated IgHV3-13 element, whereas the follicular lymphoma includes a hypermutated IgHV3-11 element. As a 3 bp footprint of the IgHV3-11 sequence is still present in the rearranged IGH gene of the B-ALL, this change appears to be the result of a BCR editing/revision process replacing the IgHV3-11-element by the upstream IgHV3-13 element during progression. In conclusion, the genetic studies indicate the clonal relationship between the two neoplasms. Development of B-ALL from follicular lymphoma is likely associated with unfavourable outcome and should therefore warrant in-depth molecular pathological examination of possible clonal relationship.

EAHP18-BMWS-241

Hypocellular common acute B-lymphoblastic leukemia misinterpreted as aplastic anemia

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Case description: 16-year-old male with 2-year history of rheumatoid arthritis (?) with considerable weight loss and weakness, pancytopenia since 14 months previously. Outside bone marrow diagnosis at onset of cytopenia: aplastic anemia (C89/14, seen retrospectively in consultation, not submitted). Further massive weight loss and B-symptoms over the course of the past year – "wasting syndrome". Repeat biopsy at our hospital after 14 months without specific therapy.
Clinical presentation: Patient in poor health, kachexia, skin lesions on trunk (lichen sclerosus?) Blood counts: Leukocytes 5.5 G/L, Hb 82 g/L, Thr. 122 G/L Differential count: Neutrophils 62.5 %, Eos 1.5 %, Basophils 2%, Lymphocytes 27%, Monocytes 5%, others 2%
Follow-up: Patient underwent chemotherapy according to AIEOP BFM ALL protocol. Allogeneic bone marrow transplant 9 months after primary diagnosis from brother. MRD recurrence, changed to Blinatumomab therapy. Multifocal osseous recurrence with relapsing course, finally manifest BM recurrence 3 years after diagnosis. Patient currently under Inotuzumab therapy, various complications and poor general health.
Biopsy fixation details: K-26849/14: Formalin fixed and decalcified with EDTA.
Frozen tissue available: no, but aspirate was sent to whole exome sequencing.
Details of microscopic findings: BM aspirate with 11% blasts, low cellularity. BM biopsy: Heterogeneous BM infiltration by blasts, ranging from less than 10% to >80%, no fibrosis.
BM biopsy from 14 months previously, seen in consultation retrospectively: very hypocellular marrow with interstitial increase in blasts.
Immunophenotype: CD34+, Pax5+, CD19+, TdT+, CD10+ MPO-, CD33-, CD117-, Lysozyme-, CD56- Identical blasts in skin biopsy and biopsy from 14 months previously.
Cytogenetics: none
Molecular studies: Identical clonal IgH rearrangement in both biopsies. Negative for BCR/ABL, TEL/AML and MLL rearrangements. WES pending.
Proposed diagnosis: Common B-ALL initially presenting with pseudo-aplastic marrow, undiagnosed and untreated for 14 months.
Interesting feature(s) of submitted case: This exceptional case of a pseudoaplastic ALL, which went untreated for more than a year and showed several unusual clinical features such as hypoplastic marrow, lack of blasts in the peripheral blood for a prolonged time, and multifocal osseous involvement with paraneoplastic rheumatoid arthritis gives a rare view on the natural course of ALL in this unusual setting. This case needs to be differentiated from acute leukaemia evolving from true aplastic anaemia and ALL preceded by an episode of peripheral aplasia/cytopenia.

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Early T-Precursor Acute Lymphoblastic Leukemia (ETP-ALL) with Megakaryoblastic Features

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Case description: A 13 year old boy presented to his PCP with several days of fevers and lower back pain. Upon presentation to the ED he was found to be pancytopenic with circulating blasts.
Biopsy fixation details: Bone marrow core biopsy fixed in Bouin's fixative.
Frozen tissue available: None available.
Details of microscopic findings: Peripheral blood smear review at the time of presentation showed a population of variably-sized blasts with open chromatin, one or more distinct nucleoli, scant basophilic cytoplasm, and variably-prominent cytoplasmic blebs. Blasts with similar morphology were seen on the subsequent bone marrow aspirate smear. Examination of the bone marrow core biopsy showed a diffuse population of blasts with very minimal residual trilineage hematopoiesis.
Immunophenotype: Immunophenotypic analysis performed on the peripheral blood specimen revealed a population of immature cells positive for CD34, CD117, CD33, CD7, CD71 (dim), CD41, and CD61, but negative for HLA-DR, CD4, CD13, and CD15, MPO, and negative for other surface T cell, and B cell markers. Subsequent flow cytometric evaluation of the aspirate material showed a predominant population of blasts positive for CD33, CD34, and CD117 with a very minor subset exhibiting co-expression of CD41 and CD61.
Immunoperoxidase studies performed on the core biopsy specimen revealed the blasts to be predominantly CD3-positive and major subset CD34-positive; rare CD61 positive cells were seen. Additional flow cytometric evaluation of the aspirate material revealed cytoplasmic CD3 (cCD3) expression on the blast population.
Cytogenetics: Conventional karyotype: 46,XY,t(7;14)(p15;q32)[5]/46,XY[15]
FISH result: nuc ish (CSF1R,RPS14,MDFIC,D8Z1,RUNX1T1,CDKN2A,ABL1,KMT2A,ETV6,TRA@/TRD@, PML,CBFB,RARA,RUNX1,BCR)x2[200].
Molecular studies: A 95 gene next-generation sequencing (NGS) panel performed on the bone marrow aspirate material showed the following pathogenic single nucleotide variants and small insertions/deletions:
ETV6 NM_001987 c.770_771insCC p.S257fs* - in 29.4% of 841 reads
EZH2 NM_004456 c.2199C>G p.Y733* - in 32.6% of 242 reads
NOTCH1 NM_017617 c.4721T>C p.L1574P- in 51.8% of 54 reads
NRAS NM_002524 c.35G>A p.G12D - in 38.2% of 843 reads
Proposed diagnosis: Early T-cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL).
Interesting feature(s) of submitted case: ETP-ALL is an overall rare, and at times challenging, diagnosis. The t(7;14)(p15;q32) chromosomal aberration has been previously reported in 10-15 cases, which have included T-ALL most commonly, but also acute myeloid leukemia (AML), and one case of B-cell acute lymphoblastic leukemia (B-ALL). While the 7p15 component of the rearrangement typically involves the T-cell receptor-gamma (TCR-gamma) gene, the 14q32 locus has been shown to carry the immunoglobulin heavy chain (IGH) gene, and in one rare case the T-cell leukemia/lymphoma 1A (TCL1A) gene (Sugimoto et al. Int J Clin Exp Pathol 2014;7(5):2615-2623). Cases of T-ALL with this chromosomal rearrangement have all been characterized by an immature thymocyte immunophenotype (CD7-positive, surface CD3-negative, and CD4/CD8-double negative) as seen in this case; however, neither megakaryoblastic morphology nor immunophenotypic evidence of megakaryocytic differentiation has been previously described. While these features initially raised suspicion for a megakaryoblastic leukemia, subsequent identification of cytoplasmic CD3 expression, and of the NOTCH1 L1574P variant at a high allele frequency together favored a diagnosis of ETP-ALL.

EAHP18-BMWS-247

CD19-negative/sIgM-positive denovo pediatric B- lymphoblastic lymphoma/leukaemia presenting with hypercalcemia and osteolytic bony lesions.

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Case description: A 13-months old infant, presented with pneumonia, fever and significant weight loss for one month. No lymphadenopathy. Work-up revealed marked hypercalcemia (corrected Ca 3.8 mmol/L). Renal and liver function test, LDH and uric acid were all normal. Chest X-ray showed diffuse lunacies in the thoracic cage, visualized scapula, humorous and clavicle. Langerhans cell histiocytosis was suspected. Skeletal survey and MRI brain revealed diffuse enhancing bony lesions involving all skeletal bones. Bilateral bone marrow (BM) biopsies and bone curettage biopsy revealed a diagnosis of B-ALL and the patient started treatment as per BFM 2009 ALL protocol.
Biopsy fixation details: Tissue biopsy formalin-fixed, paraffin-embedded sections stained with H&E. BM biopsy: AZF-fixed
Frozen tissue available: Not available
Details of microscopic findings: Peripheral blood showed mild anemia and thrombocytopenia with no definitive circulating blasts. BM aspirate showed active trilineage hematopoiesis and infiltrated with many blasts; small in size with high nucleocytoplasmic ratio, rather dense nuclear chromatin and few inconspicuous nucleoli (microblasts morphology). The blasts showed uneven distribution (~12% in left-sided aspirate and ~9% on the right side). BM biopsy showed well represented trilineage hematopoiesis with infiltration with precursor B-cells highlighted by many PAX5/CD79a-positive cells, many CD10-positive cells and increased TdT positivity. Bone curettage biopsy was suboptimal, patchy areas showed many small lymphoid cells which express CD 79a variably and are also TdT and CD10 positive.
Immunophenotype: Flow cytometry on BM revealed 19% blasts (in the blast/early haematogones gate) expressing CD45 (mod),cytoplasmic CD79a, CD10, CD38, HLADR, TdT (majority), CD9 and sIgM.The cells are negative for: CD19, cytoplasmic CD22, cMPO, CD117, CD33, CD64, CD14, CD13, CD56, sCD3, cytoplasmic CD3,CD5, CD7, CD4, CD8, CD20, CD34, surface Kappa and Lambda light chain, IgG, IgD and IgA. Hematogones comprise ~ 3%.
Cytogenetics: Normal karyotype: 46;XY
Molecular studies: Not available
Proposed diagnosis: B-lymphoblastic lymphoma/leukemia
Interesting feature(s) of submitted case: This case of infantile B-ALL has several unique features; clinically the unusual rare presentation with diffuse osteolytic bony lesions in absence of lymphadenopathy. Immunophenotypically, the loss of CD19 (a pan B-marker) is extremely rare in lymphoid neoplasms in addition to the aberrant loss of cytoplasmic CD22. The lymphoid blasts also showed asynchronous expression of immaturity marker (TdT), together with expression of maturity associated marker (surface IgM). The aleukaemic presentation together with BM infiltration pattern also served some diagnostic challenge; the percentage of counted blasts was definitely underestimated as only cells with clear blast morphology were included and it seems that some of the cells counted as lymphocytes/haematogones were actually microblasts. Such cases may be missed without utilizing multiparametric flow cytometry at initial diagnostic work-up. Very rare cases of CD19-negative denovo B-ALL in the pediatric age group were reported in the literature1; interestingly, they share almost the same clinical presentation with osteolytic bony lesions and hypercalcemia. Studying these cases at the molecular level would be important as it may define a molecularly unique subgroup of ALL-patients.

[1]Shafinaz Hussein,Kerice Pinkney,Vaidehi Jobanputra,Govind Bhagat & Bachir Alobeid. CD19-negative B-lymphoblastic leukemia associated with hypercalcemia, lytic bone lesions and aleukemic presentation. Journal of Leukemia & Lymphoma , Volume 56, 2015 -

EAHP18-BMWS-250

Lineage switch following CD19 CAR-T treatment in a patient with TCF3-ZNF384 fusion

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Case description:
The patient was a 1-year old male diagnosed with B-ALL. The leukemic blasts expressed CD19, CD22, CD10 variable (negative to dim), and CD34. CD24 was negative. Karyotyping was positive for a 12p deletion, and FISH negative for MLL, BCR-ABL, and ETV6-RUNX1 rearrangements. RNA sequencing was positive for ZNF384-TCF3 fusion.
After multiple relapses, the patient was referred for anti-CD19 CAR-T cell therapy. Following CAR-T cell infusion, the patient went into a MRD negative remission and was given a bone marrow transplant. One year following CAR-T infusion the patient relapsed with AML. The AML was clonally related to the original disease because it continued to show 12p deletion by FISH and continued to express the ZNF384-TCF3 fusion by RNA sequencing.
This represents the first reported case of lineage switch following CD19 CAR-T treatment in a patient with ZNF384-TCF3 fusion. The leukemic cells at diagnosis had an unusual phenotype that was CD10 mostly negative, and CD24 negative, a phenotype more commonly seen with MLL rearrangements.
Biopsy fixation details: The biopsy was decalcified in B+ fixative and fixed in formalin
Frozen tissue available: Yes
Details of microscopic findings:
At diagnosis and prior to CAR-T infusion, the lymphoblasts were small to medium in size with scant agranular cytoplasm and open chromatin with single prominent nucleoli. Following CAR-T, the relapse blasts were large with ample granular cytoplasm and open chromatin with multiple prominent nucleoli.
Immunophenotype:
Prior to CAR-T: CD19 variable (dim to moderate), CD22 bright, CD10 variable (negative to dim), TdT, CD34, CD38, CD58, HLA-DR bright, CD123, and CD71 dim
Post CAR-T: positive for CD13, CD33 (partial, dim), CD34 (partial), CD117 (partial), CD123, CD11b (partial), CD38 (moderate) and CD7; negative for CD19, CD20 and CD22
Cytogenetics:
Prior to CAR-T: 46,XY[1]//46,XX[19] (post-transplant chimerism)
FISH: Positive for a loss of ETV6 (12p13) signal in 20% of the cells
Post CAR-T: 46,XY[20]
FISH: Positive for a loss of ETV6 (12p13) signal in 18% of the cells
Molecular studies:
Prior to CAR-T: RNA Sequencing: TCF3 Exon 11 (ENST00000262965) - ZNF384 Exon 2 (ENST00000396795).
Post CAR-T: RNA Sequencing: TCF3 Exon 11 (ENST00000262965) - ZNF384 Exon 2 (ENST00000396795)
Proposed diagnosis: B-ALL with lineage switch to AML
Interesting feature(s) of submitted case:
The immunophenotype of ZNF384-TCF3 is similar to MLL rearranged cases with a Pre- Pro-B phenotype. The phenotype completely switched to a myeloid phenotype following anti CD19 therapy.

EAHP18-BMWS-273

De Novo, B-cell Lymphoblastic Leukemia/Lymphoma with MYC and IGH-BCL2 Translocations.

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Case description: 20 year old previously healthy woman with no history of lymphoma presented with intermittent fevers, weakness, bruising, myalgias and petechiae on lower extremities. Presented to NYP/WCMC ER with Hgb: 8.4 g/dL, HCT: 24.5 %, WBC: 23.5 K/uL (blasts: 88%), PLT: 17 K/uL. Flow cytometry showed B-ALL with blast immunophenotype: CD19+, dim CD45+, bright CD10+, HLA-DR+, TdT+, CD38+, dim CD58+, dim CD22+. During admission, patient developed rapidly rising Transaminases (AST 2322U/L; ALT: 1868U/L), Triglycerides 217 mg/dL, Soluble IL-2R 2409 pg/mL, Ferritin 59,947ng/mL, LDH 5,560 U/L, concerning for Hemophagocytic Lymphohistiocytosis (HLH). Bone marrow biopsy was performed which showed B-lymphblastic leukemia (details below) with evidence of hemophagocytosis. Patient was treated with AALL1131 chemotherapy induction protocol including methylprednisolone/dexamethasone, etoposide, vincristine and daunorubicin.
Biopsy fixation details: Fixed in Buoin's fixative, plus standard decalcification.
Frozen tissue available: Yes; Bone marrow aspirate isolate
Details of microscopic findings: The bone marrow biopsy is hypercellular (>90% cellular) showing a diffuse proliferation of interstitial blasts with round nuclei, open to slightly clumped chromatin with variably prominent nucleoli, and minimal amount of cytoplasm. Numerous mitotic figures and apoptotic cells are present throughout this proliferation. Almost no residual trilineage hematopoiesis is identified. Occasional histiocytes with hemophagocytosis are seen. The bone marrow aspirate smears showed similar findings.
Immunophenotype: Blasts were positive for CD45(dim), CD19, CD10 (bright), TdT, CD38, CD58, CD24, cCD79a, CD22 (dim), CD81 (dim), and CD9 (partial) and negative for CD34,CD20, CD21, sCD3, cCD3, MPO, CD13, CD33, CD44, CD123, CD7, CD66c, CD86, CD99, cIgM, sIgM, CD117, NG2, CD15/CD65 as well as surface immunoglobulin kappa and lambda.
Cytogenetics: Karyotype: 46,XX,t(8;14)(q24;q32),t(14;18)(q32;q21)[3]/46,XX[24]. Interphase FISH assay detected MYC gene rearrangement in 16% of cells, and IGH-BCL2 gene rearrangement in 17% of cells indicating the presence of a t (14;18) translocation.
Molecular studies: Pending.
Proposed diagnosis: De Novo, B-cell Lymphoblastic Leukemia/Lymphoma with MYC and IGH-BCL2 Translocations
Interesting feature(s) of submitted case: This is a rare case of de novo B-ALL with MYC and BCL-2 gene rearrangements, which is also associated with Hemophagocytic Lymphohistiocytosis (HLH).
Similar cases have been previously reported in the literature (eg, (i)Loghavi S, et al. B-Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma, Am. J. Clin. Path. 2015, 144:393-410. (ii)Subramaniyam S et al. De novo B Lymphoblastic Leukemia/Lymphoma in an adult with t(14;18)(q32;q21) and c-MYC gene rearrangement involving 10p13. Leukemia & Lymphoma. 2011, 52:11, 2195-2199)). These cases represent an interesting diagnostic overlap with high grade B cell lymphomas. Some authors have described these cases as High Grade TDT Positive Blastic B Cell Leukemia/Lymphoma (Loghavi S, et al).

EAHP18-BMWS-293

Early T-cell precursor lymphoblastic leukaemia/lymphoma with extensive extramedullary involvement post bilateral cosmetic breast implant

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Case description: 27 year old woman, previously healthy, mother of three children. Status post bilateral cosmetic breast implant in 2015. In spring 2017, patient noted several, up to 1 cm large nodes in her breast bilaterally. Ultrasound guided fine needle aspiration biopsy was performed which demonstrated many small lymphocytes leading to a diagnosis of "chronic unspecific inflammation" (immunophenotyping by flow cytometry not performed). During the following weeks the patient deteriorated rapidly with generalized lymphadenopathy and a large mediastinal tumor mass with "vena cava syndrome" and bilateral pleural effusions. Peripheral blood status at presentation: Hb 110 g/L, WBC 5x10(9)/L, TPK127x10(9)/L. Flow cytometric analys of pleural fluid demonstrated an immature CD34+ T-cell population (CD7+cytCD3+CD3-TdT-CD30-), highly suspicious for T-lymphoblastic lymphoma. Repeated fine needle aspiration biopsies of breast nodules and bilateral axillary lymph nodes confirmed the diagnosis of precursor T-lymphoblastic leukaemia/lymphoma with extensive bone marrow involvement (76% blast cells). Immunophenotyping by multiparameter flow cytometry (FCM) performed on the bone marrow aspirate demonstrated a phenotype consistent with "Early T-cell precursor lymphoblastic leukaemia" (ETP) [CD45dimCD34+CD7+cytCD3+CD3-CD33+CD117+CD5dim/neg, other T-cell markers negative (CD2-, CD4-, CD8-), DR+, CD38+, CD99+, TdT-, CD10-, monocytic markers negative (CD11b-, CD64-, CD36-, CD14-), MPO-, CD13-, TdT-]. Immunohistochemistry (BMB): CD34+, CD7+, CD117+, MPO-, TdT-, other T-cellmarkers negative, lysozyme negative. Cytogenetics: normal karyotype (46,XX) FISH ALL panel normal. Array-CGH screening: normal. T-PCR without evidence of clonal rearrangement. TruSight Myeloid sequencing panel (http:www.illumin.com/prducts/trusight-myeloid.html) demonstrated pathogenetic variants in the EZH2 and PHF6 genes with VAF of 31% and 29%, respectively. Patient received treatment according to the NOPHO high-risk protocol for T-ALL with start of induction therapy in July 2017. No CNS engagement at initial presentation. In clinical, morphological and flow cytometric remission after block B treatment (September 2017). Complicated clinical course during ongoing chemotherapy requiring intensive patient care; alive without evidence of relapse by January 2018.
Biopsy fixation details: Bone marrow aspirate fixed in 4% formalin.
Frozen tissue available: no
Details of microscopic findings: Cytomorphology of fine needle aspiration from breast nodes and axillary lymph nodes demonstrates many lymphoblasts.
BM imprints: 76% lymphoblasts. BM aspiration biopsy: diffuse increase of lymphoblasts; sparse residual normal hematopoesis
Immunophenotype: CD45dim CD34+ CD7+ cytCD3+ CD5dim CD117+ CD33+ CD13-
CD13-, MPO-, TdT-, CD1a-, monocytic markers negative, other T-cell markers negative
Cytogenetics: Normal karyotype (46,XX)
Molecular studies: FISH ALL panel negative. Array-CGH screening: normal
T-PCR: no clonal rearrangement
TruSight myeloid panel: pathogenetic variants in the EZH2 (VAF 31%) and PHF6 gene (VAF 29%)
Proposed diagnosis: Early T-cell precursor lymphoblastic leukaemia/lymphoma (with extensive extramedullary involvement post bilateral cosmetic breast implant)
Interesting feature(s) of submitted case: Unusual clinical presentation with initial manifestation in bilateral breast tissue post cosmetic breast implant two years before and disseminated disease at time of hospitalization.

EAHP18-BMWS-299

B-lymphoblastic leukemia with aberrant CD36 expression and IGH/CRLF2 rearrangement

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Case description: A 3 year-old male patient presents with a one week history of abdominal pain, occasional emesis, extreme pallor and fever (39^{o} C), and on clinical examination had hepatomegaly but no lymphadenopathy. His CBC was remarkable for anemia (MCV 77.8 fL, hemoglobin 5 g/dL) thrombocytopenia (platelet count 47 x 10^{9}/L) and a white blood cell count of 6.6 x 10^{9}/L. His LDH was normal (169 IU/L; reference range:100-220 IU/L) and his uric acid was <1.5 mg/dL (reference range 1.9-5.4 mg/dL). The peripheral blood smear differential includes: 10% segmented neutrophils, 4% bands, 2% meta/myelocytes, 2% blasts, 79% lymphocytes, 3% monocytes. These blasts are negative for myeloperoxidase cytochemical stain. A bone marrow examination was performed.
Biopsy fixation details: The core biopsy was placed for 2 hours in B plus fixative, and submitted after a brief (<1 hour) decalcification to processing (formalin fixation for 2 hours and than placed in the Leika ASP 300 automatic tissue processor).
Frozen tissue available: Not available.
Details of microscopic findings: The blasts noted are predominately small to medium in size, have round to irregular nuclei, open chromatin and in a subset have conspicuous one to multiple nucleoli. A small subset of these blasts had eosinophilic intracytoplasmic granules. Auer rods are not identified. The bone marrow biopsy had a cellularity of approximately 100%, and 89.3% blasts were identified in the aspirate differential.
Immunophenotype: By flow cytometry analysis of a bone marrow aspirate sample were identified 73% blasts of B-lymphoid lineage expressing dim CD45 (100%), CD34 (100%), CD10 (100%), CD20(75%), CD22 (95%), CD19(100%), CD38(100%), CD24(97%), CD38(100%), HLA-DR(99%), cytoplasmic TdT(98%), CD36(43%), and CD9(99%). They were negative for surface CD3, CD2, CD7, CD13, CD33, CD117, CD15, CD64, and cytoplasmic myeloperoxidase.
Cytogenetics: Karyotype: 46, XY[20].
Molecular studies: FISH studies were negative for MLL rearrangement, BCR-ABL1 fusion, ETV6-RUNX1, RUNX1T1-RUNX1, negative for gain of chromosomes 4, 10, 17, negative for deletion 9p21 (CDKN2A), negative for PBX1-TCF3 fusion, negative for the common cytogenetic abnormalities detected in MDS[5P15.2 (D5S23/D5S721), 5q31.2(EGR1), 7cen(DTZ1), 7q31(D7S486), 8cen(D8Z2), and 20q12(D20S108)].
FISH studies are reported positive for IgH (14q32.3) rearrangement and CRLF2 rearrangement. The last two findings suggest the IGH/CRLF2 rearrangement brought about by the a cryptic translocation t(X,14)(p22.3;q32)/t(Y;14)(p11;q32).
Proposed diagnosis: B-lymphoblastic leukemia with aberrant CD36 expression and IGH/CRLF2 rearrangement.
Interesting feature(s) of submitted case: This B-lymphoblastic leukemia has aberrant expression of CD36 and an associated IGH/CRLF2 rearrangement. The expression of CD36 on B-lymphoblasts is rarely detected (approx. 7-8% of the B-LL cases). The CD36 expression on B-lymphoblasts has been more recently reported to predict a poor outcome in children with B-lymphoblastic leukemia (Newton JG et al, 2017). CRLF2 genomic lesions have been reported almost exclusively in B-ALL cases classified as standard/intermediate risk (SR) or high risk (HR) being largely absent in in patients with low or very-high risk disease. CRLF2 genomic lesions have not yet been reported in association with aberrant CD36 expression.

EAHP18-BMWS-305

B-lymphoblastic leukemia with aberrant CD2 expression and TRA/D rearrangement

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Case description: A 3-year-old previously healthy Caucasian male patient presented with a 3-days history of extreme fatigue, pallor, and fever (39°C) and was found to have cervical and supraclavicular lymphadenopathy. His CBC was remarkable for severe anemia (hemoglobin 3.6 g/dL) and thrombocytopenia (platelet count 39 x 10^9/L), while his white blood cell count was 10 x 10^9/L. LDH was 335 IU/L (reference range 100-220 IU/L) and his uric acid was 4.4 mg/dL (reference range 1.9-5.4 mg/dL). He underwent bone marrow examination.
Biopsy fixation details: The core biopsy was placed for 2 hours in B plus fixative, and submitted after a brief decalcification to processing (2 hours formalin fixation and than was placed in a Leika ASP 300 automatic tissue processor).
Frozen tissue available: Not available.
Details of microscopic findings: His peripheral blood smear had 77% blasts of predominately small to medium size and with a small subset of large sized blasts. These blasts have round to irregular nuclei, open chromatin and in a subset they have conspicuous one to multiple nucleoli. Auer rods are not identified. These blasts are negative for myeloperoxidase cytochemical stain. The bone marrow had a cellularity of approximately 100% with the blast population reaching 96.3% on the touch preparation differential.
Immunophenotype: By flow cytometry the blast population was positive for CD45(100%), CD34(100%), CD10(98%), CD22(98%), CD79a(99%), CD19 (dim) (100%), CD38(100%), CD24(98%), CD58(97%), HLA-DR(97%), cytoplasmic TdT (79%), cytoplasmic mu (100%), CD9(66%) and CD2(99%). In a subset they are sIgM (22%). They are negative for sCD3, CD13, CD33, CD36, CD117, CD1a, CD4, CD5, CD7, cytoplasmic myeloperoxidase and also negative for cytoplasmic CD3(6%).
Cytogenetics: 46,XY[20].
Molecular studies: FISH: Positive for: T-cell alpha-delta receptor TRA/D (14q11.2); negative for: MLL, BCR-ABL1, ETV6-RUNX1, gains 4, 10, 17, del9p21, IGH (14q32.3) and TCL1.
PCR: Clonal IGH; negative TCR beta and gamma.
Microarray assay: ~2.7 MB gain Xp22.33/Yp11.32; ~296 KB loss 8q24.21.
Proposed diagnosis: B-lymphoblastic leukemia with aberrant CD2 expression and TRA/D rearrangement
Interesting feature(s) of submitted case: The lymphoblast population has a dominant B-lineage immunophenotype with aberrant expression of CD2. The additional unusual features of this case were the finding on both peripheral blood and bone marrow blasts by flow cytometry of a very small subset of blasts with cytoplasmic CD3 expression (<10%). Given the dominant B-lineage expression and WHO 2016 criteria a diagnosis of B-lymphoblastic leukemia was rendered. There are however unusual factors introduced by the minimal cytoplasmic CD3 expression by flow cytometry, the EGIL 1998 criteria for T-lineage (CD2, CD10 and TdT=2.5 points), as well as by the presence of a TCR/D rearrangement (FISH analysis) and a T-cell receptor gamma gene rearrangement detected by PCR, that brought in the differential diagnosis the concern for a mixed phenotype B/T acute leukemia. The impact of the detected loss of 8q21.21 and gain of Xp22.33/Yp11.32 in the pseudoautosomal region to the overall course of the disease remains uncertain.
The patient was treated according to a Dana Farber protocol DFCI 11-001 for B-lymphoblastic leukemia, of standard risk arm, and achieved complete remission. He remained in remission, now 3-years since his diagnosis.

EAHP18-BMWS-309

Phi (-) B-lymphoblastic lymphoma with unexpected CD5 expression and MYC/IGH rearrangement

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Case description: Clinical history:
A 52 year old man with past HCV infection (cured by elbasvir and grazoprevir) presented in August 2017 with a painful right ankle swelling, anorexia and mild weight loss. Clinical examination was otherwise unremarkable, with no lymphoadenopathy. Initial imaging workup (right ankle CT and MRI) showed bone medullary invasion by a 7 cm tissular mass centered on the lower end of the tibia, associated with periosteal reaction and extension into neighbouring soft tissues. The MRI also outlined a pathologic fracture of the lower tibia and tumoral necrosis. Body-scan, spinal tap and brain MRI were performed and didn't show involvement of other organs. However, PET-CT showed a hypermetabolism of the right ankle lesion with a SUVmax of 3.6 in the bone, up to 7.8 in the soft tissues. Concerns for an aggressive bone tumor led to a bone trephine biopsy. A second biopsy was performed to gather tissue for cytogenetics and molecular studies but did not retrieve vital tissue.
Peripheral blood counts (at onset): PLT 267 G/L, Hb 15g/dl, WBC 8G/L, PMN 4140/mm3.
Other biological data: LDH 304 UI/L (1.5N), beta2microglobulin 2.1 mg/L, polyclonal hypergammaglobulinemia 15g/L, HIV serology negative.
Bone marrow trephine biopsy and myelogram (16/11/2017): no involvement.
Biopsy fixation details: and decalcification details: biopsy fixation in neutral buffered formalin for 24 h and decalcification in EDTA for 48 hours at 37°C.
Frozen tissue available: material not suitable
Details of microscopic findings: Bone trabeculae showed signs of bone remodelling and were massively occupied by monotonous medium-sized cells with round nuclei, often notched, inconspicuous chromatin and eosinophilic central nucleoli in most cells, with scant cytoplasm; there were scattered tingible body macrophages in the background. Mitoses were readily seen as well as foci of necrosis.
Immunophenotype: Tumor cells were CD20(+), PAX5(+), CD79a(+), TdT(+), CD5(+), Bcl2(+). CD10 was expressed with moderate intensity. Other markers were negative (CD34, Bcl6, Myc, CD30, CD23, MUM1, cyclinD1, SOX11). Ki67 was estimated at 70%. EBERs were negative (ISH).
Cytogenetics: (Fluorescent in-situ hybridization): MYC was rearranged with IGH as a partner. BCL2, BCL6, BCR/ABL showed no rearrangement.
Molecular studies: material not suitable
Proposed diagnosis: Phi (-) B-lymphoblastic lymphoma with unexpected CD5 expression and MYC/IGH rearrangement
Interesting feature(s) of submitted case: Interesting feature(s) of submitted case: this case was a diagnostic challenge because of its clinical presentation as a solitary bone lesion. Overmore, the morphology was reminiscent of a blastoid aggressive lymphoproliferation, with CD5 positivity which raised concerns for a blastoid mantle cell lymphoma: however both, cyclinD1 and SOX11 were negative. Immunophenotype was not compatible with Burkitt lymphoma (Bcl2+, Bcl6-, Ki67 as low as 70%). A high grade B-cell lymphoma was discussed but positivity of immature lymphoid cell markers such as TdT and CD10 favored the current diagnosis. CD34 negativity was unexpected but such finding has been reported in literature.
Comments: the patient is undergoing intensive ALL-like chemotherapy protocol. He had partial metabolic response on day 40 PET-scan with a decrease in uptake value of the tibial lesion (SUVmax 4.2 vs 8.7).

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Acute leukemia of ambiguous lineage: An unusual B-lymphoblastic leukemia masquerading as a blastic plasmacytoid dendritic cell neoplasm?

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Case description: A 64-year-old man presented with fatigue, night sweats, and weight loss and was found to have a nodular rash and lymphadenopathy. CBC showed pancytopenia and 15% blasts. Peripheral blood flow cytometry, skin biopsy, and bone marrow core biopsy were performed.
He went into remission following chemotherapy. One year later, a new nodular rash appeared and a bone marrow biopsy showed relapsed disease. Salvage chemotherapy was unsuccessful and the patient died soon thereafter.
Biopsy fixation details: Skin biopsy is formalin fixed. Bone marrow biopsy is B5 fixed and decalcified.
Frozen tissue available: No.
Details of microscopic findings: Skin biopsy
H&E stained sections show skin with a perivascular and periadnexal dermal infiltrate of medium-sized cells with round to oval nuclei, fine chromatin, prominent nucleoli and scant cytoplasm. Numerous apoptotic bodies are present.
Bone marrow biopsy
H&E stained sections show a markedly hypercellular bone marrow completely replaced by sheets of medium-sized cells with round to oval nuclei, fine chromatin, prominent nucleoli, and scant cytoplasm. Numerous mitotic figures and apoptotic bodies are present.
Immunophenotype: Peripheral blood
Flow cytometry reveals a population (12% of total events) of large CD4+ HLA-DR+ and CD123(dim)+ cells, that are negative for CD56, TdT, CD34, and other B-cell, T-cell, and myeloid markers.
Skin
The atypical cells are positive for CD45, CD79a, CD123, TCL1, PAX5, and CD4(dim) and are negative for CD1a, CD3, CD5, CD8, CD10, CD20, CD21, CD23, CD34, CD35, CD56, CD45RO, CD117, CD138, lysozyme, MPO, and TdT.
Bone marrow
Identical to that in the skin.
Cytogenetics: Bone marrow (initial diagnosis): 47,XY,+8 [5]
Bone marrow (relapse):
45-47,XY,del(6)(q13q25),+del(6)(q13q25),add(12)(p11.2),add(13)(p11.2), add(18)(p11.2)cp[7]/46,XY [15]
Molecular studies: TRG and IGH PCR: both negative for a monoclonal rearrangement.
Proposed diagnosis: Acute leukemia of ambiguous lineage with features of a blastic plasmacytoid dendritic cell neoplasm and B-lymphoblastic leukemia
Interesting feature(s) of submitted case: The initial putative diagnosis was blastic plasmacytoid dendritic cell neoplasm (BPDCN) based on a classic hematodermic presentation and expression of CD4, CD123 and TCL1. However, the expression of B-cell antigens (CD79a and PAX5) is unusual, which, in addition to the lack of CD56 (rarely absent in BPDCN) raised the consideration of a B-lymphoblastic leukemia (B-ALL), noting that both CD123 and TCL1 are expressed by B-cell subsets. However, the immunophenotype is unusual for B-ALL too, given the lack of TdT, CD10, CD19, CD20, and CD34. Cytogenetic studies at diagnosis revealed +8, which is usually associated with myeloid neoplasms; however, the +8 was not evident at relapse. Abnormalities of 6q deletion have been described in both B-ALL and BPDCN. In conclusion, the unusual immunophenotype of this peculiar neoplasm is not specific for one entity, and may be best classified as an acute leukemia of ambiguous lineage with features of a B-ALL and BPDCN.
NOTE: The submitted glass slides are from the skin biopsy. The tissue in the bone marrow biopsy was unfortunately exhausted

EAHP18-BMWS-393

B-lymphoblastic leukemia with BCL-2 and MYC gene rearrangement and atypical phenotype

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Case description: A 68-year-old male initially presented with increased fatigue and weakness for two weeks. He was sent to local ED due to altered mental status. Laboratory study showed mild leukocytosis (14.8 x 10^9/L) and thrombocytopenia (44 x 10^9/L). Peripheral blood (PB) specimen was sent for flow cytometry (FCM) and a subsequent bone marrow (BM) biopsy was performed (results see below). Chest X-ray showed bilateral pneumonia. Brain MRI showed a small subdural hematoma (0.4 cm) in left occipital lobe and subacute left caudate infarct which precluded a lumbar puncture evaluation. He was transferred to our institute for medical management. Further abdominal and pelvic CT did not reveal lymphadenopathy or organomegaly. Despite intensive care, the patient expired 30 days after the initial diagnosis.
Biopsy fixation details: NA (outside BM)
Frozen tissue available: NA
Details of microscopic findings: The BM aspirate smears are composed of sheets of neoplastic cells, medium to large in size, with fine to condensed chromatin, prominent nucleoli, and scant basophilic cytoplasm. Cytoplasmic vacuoles are present in some cells. The BM core biopsy shows hypercellularity and is packed with sheets of immature mononuclear cells (80%). Examination of PB smear reveals a number of circulating atypical lymphoid cells, morphologically similar to those identified in the BM.
Immunophenotype: The initial FCM detected a population of cells in blast gate (6-7% in PB and 70% in BM) which were dim CD45+/CD19+/CD10+/surface CD22+/CD38+/HLA-DR+. These cells lacked CD20, CD34 and light chain expression. Immunohistochemical (IHC) stains showed that the cells were positive for CD79a and PAX5 and negative for CD34. Only a small subset of the cells was positive for TdT.
FCM was repeated on the patient's PB at our institute, which showed the similar findings. The neoplastic cells (66% of total events) were CD10+/CD19+/CD22+/CD38+/cytoplasmic CD79a+ and CD20-/CD34-/cytoplasmic CD22-/TdT-/MPO-/surface and cytoplasmic light chains-. Small populations of reactive T /NK cells (10%) and rare B-cells (1%) were noted.
Cytogenetics: Cytogenetics showed complex cytogenetic abnormalities:
47,XY,+X,dup(1)(q21q32),t(8;22)(q24.1;q12),-9,del(9)(p10),i(13)(q10),t(14;18)(q32)(q21),+20,+21[cp15]/46,XY[5]. FISH study performed on his PB specimen confirmed the presence of IgH/BCL2 rearrangement (81%) and MYC rearrangement (71.5%). There were no MLL/KMT2A or BCR/ABL1 rearrangements identified. One extra BCR signal was found in 65.5% of nuclei examined.
Molecular studies: NA
Proposed diagnosis: B-lymphoblastic leukemia (B-ALL) with BCL-2 and MYC gene rearrangements and atypical phenotype
Interesting feature(s) of submitted case: B-ALL with BCL-2and MYC rearrangements is very rarely encountered, which should be distinguished from high grade B-cell lymphoma with BCL-2 and MYC rearrangements (double-hit) (2016 WHO classification) by TdT or CD34 expression and a distribution mainly restricted to BM and/or PB, though extramedullary sites can also be involved. Our patient had a very aggressive clinical course with numerous circulating blasts, many of which morphologically resemble high grade lymphoma cells, and phenotypically lack CD34 and TdT expression by FCM, rendering a diagnostic challenge. However, a predominant PB and BM involvement without lymphadenopathy and organomegaly, dim CD45 expression and CD20 negativity by FCM, and TdT positivity in a subset of the cells by IHC make it more compatible with B-ALL than double hit lymphoma. Interestingly, there seems to be a maturing process of the neoplastic cell with regard to morphology ranging from fine to condense chromatin pattern.

EAHP18-BMWS-412

A child with B-cell leukaemia/lymphoma with IGL-MYC t(8;22) rearrangement showing overlapping features of B-lymphoblastic lymphoma/leukaemia and Burkitt lymphoma.

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Case description: Four years old female. Past medical history: She was born to a HIV-positive mother and was delivered by C-section and received antiretroviral treatment from birth. HIV test at one year was negative. Present history: Admitted to hospital with three week history of back and joint pains, malaise and abdominal swelling. Lab studies revealed anaemia, thrombocytopenia and high white count. HIV test was negative. CT scan demonstrated hepato-splenomegaly, prominent jugulodigastric, axillary, left supraclavicular and inguinal lymph nodes as well as multiple lytic bone lesions, predominantly within the sternum and pelvis.
Biopsy fixation details: Bone marrow trephine sample was fixed with 10% formalin and decalcified with EDTA.
Frozen tissue available: N/A
Details of microscopic findings: Peripheral blood film and bone marrow aspirate showed large blasts with basophilic cytoplasm and vacuoles.
Bone marrow trephine showed high volume involvement by medium to large-sized lymphoid tumour cells with nuclei displaying round/ slightly irregular nuclear outlines, evenly-distributed chromatin and nucleoli. Frequent apoptotic bodies and scattered mitotic figures were detected.
Immunophenotype: The neoplastic cells display the following immunophenotype: CD19+, CD79a+, CD79b-, CD20+ (weak), PAX5+, CD10+, BCL6-, BCL2-/+, C-MYC protein+ (>90%), CD9+ (strong), CD22+ (strong), CD33+ (weak), CD38+ (strong), CD11b+, CD43+ (strong), CD81+ (strong), CD99+, CD45+ (weak), TdT+, HLA-DR+ (strong), cyIgM+, cyclinD1-, CD34-, CD117-, CD3-, CD5- and EBV- (EBER ISH). No surface immunoglobulin light chain expression was detected.
Proliferation index: ~70% (Ki67).
Cytogenetics: 46,XX,t(8;22)(q24;q11)[8]/46,XX[2]
Molecular studies: FISH:
Positive for MYC (8q24) rearrangement.
Positive for IGL (22q11) rearrangement.
Negative for IGH-MYC t (8;14) and IGH-BCL2 t(14;18) rearrangements.
Negative for rearrangement of IGK (2p12) and BCL6 (3q27).
Negative for BCR/ ABL1, MLL and ETV6/ RUNX1.
Proposed diagnosis: Proposed diagnosis: B-cell leukaemia/lymphoma with immunophenotype most consistent with B-lymphoblastic lymphoma/leukaemia with IGL-MYC t(8;22) rearrangement.
Interesting feature(s) of submitted case: There are overlapping features some of which suggest an immature lymphoblastic proliferation (B-lymphoblastic lymphoma/leukaemia) while others would be more in favour of a mature B-cell lymphoma such as Burkitt lymphoma. Similar rare cases have been described in the literature and the updated WHO classification categorises these as a variant of Burkitt lymphoma. However, the phenotypic features such as the TdT expression and weak CD20 expression as well as the lack of BCL6 and surface light chain expression would favour B lymphoblastic lymphoma/leukaemia over Burkitt lymphoma.

EAHP18-BMWS-413

BCR-ABL1 positive pre-T-cell lymphoblastic leukemia/lymphoma.

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Case description: A 33-year-old male presented to an outside hospital with shortness of breath. A workup revealed an elevated white blood cell count (WBC) with circulating blasts. Subsequent bone marrow biopsy was diagnostic for T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) and he was transferred to UAB Hospital for escalation of the clinical course. Upon admission he had a WBC of 47.2 x 10 cells/mL with circulating blasts and diffuse lymphadenopathy. After initial treatment in July 2015, the patient refused further therapy and was lost to follow up. He re-presented on October 2017 with similar symptoms and findings. He was treated with prednisone and dasatinib and is currently in remission.
Biopsy fixation details: The biopsy tissue was fixed in formalin, briefly decalcified, embedded in paraffin, and 3µ thick sections were mounted and stained using routine hematoxylin & eosin stain.
Frozen tissue available: Not performed.
Details of microscopic findings: Bone marrow biopsy revealed a hypercellular marrow (95%) consisting primarily of immature blasts (80% of total cells). The aspirate and touch imprint showed immature blasts with rare cytoplasmic vacuoles and large nuclei with finely distributed chromatin.
Immunophenotype: Flow cytometry (bone marrow)
The blasts were positive for cytoplasmic (c) CD3, CD5, CD7, CD10heterogeneous, CD33, and CD34 and negative for CD2, CD3, CD4, CD8, TCR gamma/delta, TdT, CD13, CD117, cMPO, HLA-DR, CD19, CD20, cCD79a, CD15, CD64, CD14, CD56.
Cytogenetics: Abnormal male karyotype with 97% of the cells having the t(9;22)(q34;q11.2) translocation.
Molecular studies: BCR/ABL1 gene fusion was detected with 89% of these cells having an extra fusion signal, possibly due to the presence of an extra (second) derivative chromosome 22 (Philadelphia chromosome). No other chromosome abnormalities were detected. A breakpoint in the m-BCR region resulting in $p190^{BCR\text{-}ABL}$protein was detected.
Proposed diagnosis: BCR-ABL1 positive pre-T-cell lymphoblastic leukemia/lymphoma (T-ALL).
Interesting feature(s) of submitted case: This is a unique case of BCR-ABL1 gene fusion in a case of pre-T-ALL with bone marrow and (clinically) lymph node involvement. The Philadelphia chromosome (Ph) is most notably found in chronic myelogenous leukemia (CML) and also in some cases of pre-B-ALL. On the contrary, the presence of BCR-ABL1 gene fusion in T-ALL is extremely rare with only few cases reported in the literature. BCR-ABL positive T-ALL is usually due to a T-lymphoid blast phase of CML. It is difficult to distinguish de novo BCR-ABL positive T-ALL from the ones arising from CML. Clinical and molecular features can help to guide one in distinguishing these two entities. Features favoring de novo T-ALL include younger age, p190 transcripts, and fluorescent in situ hybridization (FISH) studies demonstrating BCR-ABL1 fusion exclusively in lymphoblasts all of which are present in the current case. This case highlights a common genetic mutation occurring in an uncommon setting with important prognostic and therapeutic implications. BCR-ABL-positive T-ALL is often associated with poor prognosis and required stem cell transplant. Interestingly, despite the suboptimal therapy due to refusal by the patient, a remission was reached initially in this patient and lasted several years.

EAHP18-BMWS-458

Methodology and Variance in Myeloperoxidase Positivity in a Patient with cCD3-positive, Myeloid Marker-positive Acute Leukemia

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Case description: The patient is an 18 year-old, previously healthy male who presented with a three week history of sore throat and cervical lymphadenopathy. Chest x-ray showed no infiltrates and no mediastinal lymphadenopathy. A complete blood count showed a white cell count of $49.5x10^9$/L with 67% blasts, a hemoglobin of 7.9g/dL, and platelets of $78x10^9$/L. A trephine core biopsy was collected along with peripheral blood and cerebrospinal fluid. After diagnosis, the patient was admitted for induction chemotherapy.
Biopsy fixation details: A right posterior iliac bone marrow biopsy was decalcified in Bouin's fixative and processed for paraffin embedding.
Frozen tissue available: Frozen tissue is not available.
Details of microscopic findings: Microscopic evaluation demonstrated abundant immature cells with scant cytoplasm, dispersed chromatin, and indistinct nucleoli, consistent with blasts. (Figs 1-3) Maturing erythroid and myeloid cells were markedly decreased. Megakaryocytes were rare but morphologically unremarkable.
Immunophenotype: Flow cytometry showed blasts to co-express cCD3, CD2, CD7, TdT, CD99, CD34, CD117, HLA-DR, CD13, and CD15 (subset). A very small subset (2.9%) of CD34+, CD117+ cells were seen to be variably positive (dim to strong) for myeloperoxidase (MPO). (Fig 4) Immunohistochemical studies showed blasts to be positive for CD3, CD2, CD7 (dim), TdT, CD34, and CD117 and negative for CD1a, CD5, CD4, and CD8. MPO was strongly positive in 10% of blasts (Figs 5&6).
Cytogenetics: A normal male karyotype, 46,XY (Fig 7) was detected by conventional cytogenetics. Fluorescence in situ hybridization was negative for RUNX1T1/RUNX1, BCR/ABL1, KMT2A (MLL), ETV6/RUNX1, PML/RARA, CBFB and E2A (TCF3) rearrangments and negative for monosomies 5 and 7, trisomy 8, and partial deletions of 5q and 7q.
Molecular studies: A targeted next-generation sequencing assay detected a WT1 c.1300-1300insTAAGGGATCT (p.S433fs*) frameshift mutation in 42.6% of reads and two FLT3 internal tandem duplications of 36 base pairs each, with a variant allele frequency of one duplication of approximately 20.5%. (Fig 8).
Proposed diagnosis: Mixed-phenotype acute leukemia, T/myeloid (MPAL).
Interesting feature(s) of submitted case: This case highlights the delicate border separating the diagnoses of mixed-phenotype acute leukemia, T/myeloid (MPAL) and early T cell precursor acute lymphoblastic leukemia (ETP-ALL) in young adult patients and underscores the absence in the WHO 2016 Revision of a lower limit for defining myeloperoxidase (MPO) positivity in this diagnostic arena. In light of the broad variances in sensitivities for MPO detection by evaluative methodologies, we followed a strategy of multimodal diagnostic testing for MPO in this case and showed that the small (<3%) MPO-positive blast population by flow cytometry was positive at a substantially higher frequency (10%) by immunohistochemical methods.
Of note, while molecular profiles of MPAL, T/myeloid, and ETP-ALL have been recently described, they bear overlapping features, including low frequencies of ALL-type lesions including NOTCH1 activating mutations and mutations in CDKN1/2 genes and relatively high frequencies of myeloid-type lesions including FLT3, seen in this case, and RAS family gene mutations, complicating the distinction of these entities by molecular testing alone.
The diagnosis of MPAL, T/myeloid, connotes a poor prognosis and, in contrast to ETP-ALL, at our institution, is treated with prophylactic cranial radiation in addition to the standard high-intensity chemotherapy regimen, underscoring the clinical importance of the differentiation of these entities.

EAHP18-BMWS-462

B-lymphoblastic leukemia with MLL gene rearrangement with transdifferentiation to monocytic lineage in complete remission with CD19 specific CAR T cell immunotherapy

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Case description: A 3-year-old girl presented with high-grade fever (100.5F) and epistaxis in April 2012. CBC showed leukocytosis, anemia, thrombocytopenia with 85% blasts (WBC:286 K/ul; Hgb: 6g/dl; platelet count: 13K/ul). Bone marrow (BM) revealed extensive involvement by B-lymphoblastic leukemia/lymphoma (CD19+, CD22+, TdT+, CD33+ immunophenotype). Cytogenetic abnormality of t(4;11) was detected. FISH studies detected MLL gene rearrangement (11q23). She was treated with NYII protocol and completed her course in May 2015. Six months later, she presented with low-grade fever and peripheral blood examination revealed 7% blasts. Flow cytometry showed relapsed disease with similar immunophenotype as the previous biopsy. Despite treatment, she had persistent disease. Repeat BM biopsy revealed an abnormal immature population of blasts with B and monocytic differentiation.Aspirate smears revealed 46% blasts with promonocytes/monoblasts admixed with lymphoblasts. Cytogenetics studies detected pericentric inversion of chromosome 2 and t(4q;11q); FISH studies showed MLL gene rearrangement. NGS based assay identified KRAS G13D; MLL MLL-AFF1 (AF4) fusion and MSH2 R406*. She received CAR T cell immunotherapy. Follow up BM and FISH studies were negative. She underwent an unmodified BM transplant and remained in MRD- CR, status post-transplant 21 months.
Biopsy fixation details: Biopsy was decalcified and fixed in 10% formalin
Frozen tissue available: NA
Details of microscopic findings: Core biopsy and aspirate smears showed normocellular marrow with marked increase in promonocytes/monoblasts that were medium-large sized with folded nuclei, finely stippled chromatin, prominent nucleoli and moderate amount of cytoplasm admixed with lymphoblasts
Immunophenotype: Immunohistochemical stain showed two different populations of blasts. 1st component (B lymphoblastic blasts) strongly expressed CD34 and CD19 (<5% of cellularity); 2nd component with a monocytic morphology that expressed CD11c and CD33. Flow cytometry confirmed the presence of abnormal B and expanded immature monocyte populations. Immature B cells (8.7% of WBC) abnormally expressed CD10 (negative), CD19 (bright), CD34 (negative to bright), CD38 (dim to bright), bright CD123 and HLA-DR; immature monocytes (9.5% of WBC) expressed HLA-DR, CD64, CD15, dim CD11b and lacked CD14. Dim CD19 expression was seen on a subset of CD64 and CD33 positive monocytic forms with immature features.
Cytogenetics: Clonal cytogenetic abnormalities included a pericentric inversion of chromosome 2 and t(4q;11q). FISH dual probe break-apart (Abbott Molecular) detected MLL gene (11q23) rearrangement
Molecular studies: NGS based assay detected KRAS G13D; MLL MLL-AFF1 (AF4) fusion and MSH2 R406*
Proposed diagnosis: B-lymphoblastic leukemia with MLL gene rearrangement with transdifferentiation to monocytic lineage on therapy
Interesting feature(s) of submitted case: MLL gene rearrangements are associated with an extremely poor prognosis in patients with acute lymphoblastic leukemia (ALL). Transdifferentiation from the lymphoid to monocytic lineage during B lymphoblastic leukemia treatment is considered rare. Here, we describe a unique case of a 3-year-old girl with a history of persistent B-ALL with MLL gene rearrangement, a subset of lymphoblast transdifferentiated into monocytic lineage during treatment. This phenomenon may be triggered by alterations in lineage-determining transcription programs, which results in transdifferentiation coupled with oncogenic stimuli caused by chromosomal imbalances

EAHP18-BMWS-477

B-lymphoblastic leukemia/ lymphoma with clonal progression and immunophenotypic shift to myeloid blasts

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Case description: 58-year-old female with a long standing h/o HIV, well-controlled on HAART, presented with pancytopenia (WBC: 0.6 K/MCL; ANC:0.1k/MCL; Hgb:7.8 g/dl, MCV:105fl, Platelets:26 K/MCL). Bone marrow (BM) biopsy showed findings concerning for early myelodysplastic syndrome (MDS), while a molecular panel and cytogenetic studies were negative. She was followed closely. 10 months later, she presented with fever and cytopenias. BM revealed sheets of blasts (74%), immunophenotype consistent with B-lymphoblastic leukemia/ lymphoma (B-ALL). Karyotype showed t(2;10) in addition to trisomy 8 and deletion of ETV6 (12p), which were confirmed by FISH; BCR-ABL fusion was negative. Molecular panel demonstrated ASXL1 p.E801* (VAF 34%) gene mutation. She was treated on a B-ALL protocol. On completion of induction follow-up BM revealed few suspicious immature B-blasts by flow cytometry (FC) only. At the re-induction phase, B-ALL persisted (0.47% by FC, 5% by aspirate) and she was started on blinatumomab. At completion, BM showed 75% blasts positive for MPO, consistent with acute myeloid leukemia (AML), and no evidence of B-lymphoblasts. Molecular and cytogenetic studies showed similarities to the B-ALL. Retrospective molecular studies were performed on MDS BM and we identified that MDS, B-ALL and AML BM's all shared the same clone and were clonally related. Despite treatment, she succumbed to her disease
Biopsy fixation details: Decalcification, 10% formalin fixation
Frozen tissue available: NA
Details of microscopic findings: Initial (1) leukemic blasts were intermediate in size, with round to oval nuclei, fine chromatin, prominent nucleoli and variable amount of cytoplasm. Blasts with myeloid differentiation (2) showed similar morphology but were characterized by numerous cytoplasmic vacuoles
Immunophenotype: By FC, initial leukemic blasts (87.6%) were positive for bright expression of CD19, CD34, CD58, CD33, CD123, CD20 (subset), CD13, CD38, cCD79a and HLA-DR and negative for CD10, MPO, cyCD3, CD11b, CD14, CD64. After blinatumomab, blasts by immunostaining were strongly positive for CD34; while TdT was negative. FC detected abnormal myeloid blasts (61.4%) with expression of MPO (subset) with bright CD33, CD34, CD11b (dim), CD15 (dim), CD64 (dim); negative for CD13, CD117, CD2, cCD3, CD5, CD7, CD8, CD10, CD19, CD20, CD56, cyCD79a. No abnormal immature B cell population was detected.
Cytogenetics: Original karyotype:47,XX,t(2;10)(p?21;q?24),+8,del(12)(p12)x?2 [7]/46,XX [16]. Blasts with myeloid profile: 47,XX,t(1;3)(q25;q21),t(2;10)(p?13;q?24),+8,?add(12)(p11.2)[20]
Molecular studies: 30 gene myeloid panel detected ASXL1 p.E801* initially at VAF 34% and subsequently at 4%. Interestingly, the IGH gene rearrangement present at the initial leukemic presentation was detected in the leukemic blasts with a myeloid immunoprofile.
Proposed diagnosis: B-lymphoblastic leukemia/ lymphoma with clonal progression and immunophenotypic shift to myeloid blasts shares the identical clone
Interesting feature(s) of submitted case: This case represents an unusual immunophenotypic switch from a lymphoid to myeloid leukemia. Based on the cytogenetic and retrospectively performed molecular analysis, demonstrates all 3 diseases (MDS, B-ALL, AML) shared the identical clone and hence suggests the same underlying stem cell disorder. Such cases are rare and most commonly associated with MLL gene rearrangements; they are often refractory to therapy and portend a poor prognosis. To the best of our knowledge, this case with refractory/relapsed B-ALL and immunophenotype switch following initiation of blinatumomab therapy has not been described in the literature

EAHP18-BMWS-479

Gamma Delta T lymphoblastic leukaemia

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Case description: 20 month female presented with upper airway obstruction due to massive tonsillar enlargement and tumour lysis syndrome. She had no mediastinal mass, hepatosplenomegaly or lymphadenopathy. Her FBE showed a WCC of 258 x 10e9/L with 70% blasts, morphologically consistent with lymphoblasts. Following confirmation of diagnosis she was treated with AALL1321 protocol. Induction was complicated by myositis and venous thrombosis. She did not achieve CR at day 29 with residual disease evident by flow cytometry and FISH / cytogenetics. Consolidation was commenced following wide consultation including COG, with a view to SCT if CR could be achieved. She developed candida sepsis in the setting of profound neutropenia and suffered a cardiac arrest. ECMO support was instituted but there was no recovery of cardiac function and treatment was withdrawn.
Biopsy fixation details: Buffered Formalin
Frozen tissue available: No
Details of microscopic findings: Aspirate - ~ 60% intermediate sized blasts with fine chromatin, 1- 2 nucleoli and scant to small amount of pale blue cytoplasm.
Trephine – moderate to heavy infiltrate of intermediate to large blasts with scant to small amount of cytoplasm. Blasts show CD3 and CD5 positivity; CD4 / 8 / 56 / 34 / TIA are negative
Immunophenotype: Bone Marrow – left and right
POSITIVE: CD2 (weak to negative), CD3 (strong), CD5, CD7 (strong), CD11b, CD13, CD45, CD117 (subset) and gamma-delta TCR
NEGATIVE: CD1a, CD4, CD8, CD19, CD30, CD56, alpha-beta TCR, cytoplasmic TDT, cytoplasmic MPO
Cytogenetics: 46XX,t(8;14)(q24;q11.2),del(9)(p16)
Molecular studies: FLT3 JM Domain ITD mutation not detected
Proposed diagnosis: Gamma delta T – Lymphoblastic Leukaemia / lymphoma
Interesting feature(s) of submitted case: This is a rare form of leukaemia, accounting for 2% of lymphoblastic leukaemia and~ 10% of T – LL. It has a high risk of failure of induction and poor outcome.
The phenotype if viewed in isolation may mislead diagnosis, as it is a pattern more commonly seen in mature T cell LPD/ Lymphoma, demonstrating the importance of correlation with morphological and clinical information.
The t(8;14)(q24:q11.2)is very rare in T lymphoblastic Leukaemia / Lymphoma. It is associated with high white cell count. In this case it appears that the breakpoints have resulted in inactivation of alpha beta TCR expression with preferential up regulation of TCG gamma delta.

EAHP18-BMWS-485

Philadelphia chromosome positive acute lymphoblastic leukaemia arising in Waldenstrom's macroglobulinaemia

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Case description: We present a 66-year-old with BCR-ABL associated B acute lymphoblastic leukaemia (Ph+B-ALL) arising 14 years after diagnosis of lymphoplasmacytic lymphoma (LPL).
The patient presented with anaemia and an IgM kappa paraprotein in 2003. Bone marrow biopsy (BMAT) showed a diffuse infiltrate of CD79a+ CD20+ CD10- CD5- CyclinD1- kappa-restricted small B-cells with lymphoplasmacytic morphology. Single-agent chlorambucil in 2005 resulted in a disease control for 5 years. At first relapse, she received rituximab and chlorambucil. The disease again progressed in 2013 and the patient attained a PR on rituximab and bendamustine on the MABCUTE trial.
Four years later, the patient presented with neuropathic symptoms. The haemoglobin was 115g/dL; leukocytes $4.21x10^9$/L; lymphocytes 1.9 $x10^9$/L;neutrophils $1.41x10^9$/L; platelets $81x10^9$/L and IgM 5.9g/L.
Following BMAT (described below), the UK-ALL 60+ protocol chemotherapy and imatinib (tyrosine kinase inhibitor) was started. Despite morphological remission post-induction, the t(9:22) translocation remained detectable in 5/200 cells. After 3 months of imatinib, BCR:ABL transcript ratio was 0.034%.
Six months following the Ph+ B-ALL diagnosis, her neuropathic symptoms progressed, consistent with an infiltrative plexopathy. Superficial peroneal nerve biopsy showed no lymphoid infiltrate or amyloid deposition but BMAT revealed a nodular infiltrate of small lymphoplasmacytic cells expressing CD20+ CD79a+ and negative for blast markers, confirming LPL relapse. Clonal immunoglobulin heavy chain gene rearrangements were detectable. Currently, the patient is receiving ibrutinib (oral Bruton's tyrosine kinase inhibitor) for relapsed LPL.
(Genomic findings below refer to diagnostic BMAT; serial images provided)
Biopsy fixation details: After decalcification, the trephine specimen was embeddedin paraffin wax and 2um sections cut on a microtome. Staining was performed according to local standard operating procedures.
Frozen tissue available: None available.
Details of microscopic findings: Microscopic description of the aspirate:
Particular aspirate with hypercellular particles and trails. Erythropoiesis is reduced with all stages of maturation present. Myelopoiesis is markedly reduced. Megakaryocytes are reduced with normal morphology. There is an extensive infiltrate of blasts with open nuclear chromatin, some of which have visible nucleoli.
Microscopic description of the trephine:
This is an excellent quality trephine containing a hypercellular marrow in which the normal architecture is replaced by a diffuse infiltrate of medium sized blasts, many with prominent nucleoli. Normal trilineage haematopoiesis is markedly reduced.
Immunophenotype: Flow cytometry: Positive for CD19, CD10, CD34, HLADR, weak CD25, weak IgM, cyt TDT. Negative for CD7, CD33, CD15, CD117, CD13, CD20, NG2, cyt MPO, cyt CD3.
Immunohistochemistry: Positive for CD19, CD79a, CD10, TDT, BCL2. Negative for CD20, CyclinD1, CD5, MPO, MUM1
Cytogenetics: FISH: BCR-ABL rearrangement in 90/100 cells.
Karyotyping: 46,XX, -2+?8, t(9;22)(q34;q11),+der(14_t(2:14)(p13;q32)[4]/46,xx[2]/
Molecular studies: BCR:ABL e1a2 42%
Proposed diagnosis: BCR:ABL associated B acute lymphoblastic leukaemia
Interesting feature(s) of submitted case: Acute leukaemia complicating LPL is extremely rare. Literature review identified two previous cases of B-ALL following LPL, neither of which report molecular findings or clinical outcomes [1,2.]
References:
1 N. Angelopoulos, G. Camerone,et al. Haematologica, 74 (1989), 309-12
2 R. A. Madan, V. T. Chang, C. et al. Leukemia, 18 (2004), 1433-35

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Histiocytic sarcoma arising as transdifferentiation of B-lymphoblastic leukemia in a 61-year-old woman.

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Case description: The patient was a 61-year-old woman diagnosed in 06/2016 with B-lymphoblastic leukemia (B-ALL), not otherwise specified, involving the bone marrow. Hyper-CVAD was started and complete remission obtained after 1 cycle. In 03/2017, after three cycles of Hyper-CVAD, a bone marrow biopsy (BMB) showed relapsed B-ALL. HyperCVAD was suspended and blinatumomab initiated. In early 04/2017, a repeat BMB showed a neoplastic histiocytic population consistent with histiocytic sarcoma but no evidence of B-ALL. At the end of April, a fourth BMB showed relapsed overt B-ALL. At that point, therapy was switched to a modified POMP regimen but the patient died in 07/2017 due to complications of sepsis.
Biopsy fixation details: BMBs were fixed in B+ fixative and decalcified with Rapid Cal immuno solution.
Frozen tissue available: No
Details of microscopic findings: BMB 06/2016 (first diagnosis): Cellularity 100%, with sheets of medium-sized B lymphoblasts with prominent nucleoli and scant cytoplasm comprising >95% of cells.
BMB 07/2016: Maturing trilineage hematopoiesis with no evidence of residual B-ALL.
BMB 03/2017 (recurrent B-ALL): Cellularity 90%, with sheets of B lymphoblasts comprising approximately 90% of cells.
BMB early 04/2017: Cellularity 25% with chemotherapy effects and only rare maturing hematopoietic elements and no evidence of B-lymphoblasts. Numerous large histiocytic cells with folded to convoluted nuclei and abundant pink cytoplasm comprise 80% of the cellularity. Scattered mitotic figures are noted.
BMB late 04/2017: Cellularity 60% with sheets of B lymphoblasts comprising 95% of cells. No evidence of neoplastic histiocytic proliferation.
Immunophenotype: B-ALL at diagnosis (06/2016) and recurrence (03/2017 and late 04/2017):
CD19+/TdT+/HLADR+/CD34+/-/CD38+/CD20-/CD10- without surface light chain expression by flow cytometry; PAX5+/MYC+/p53+ by immunohistochemistry.
Histiocytic sarcoma (early 04/2017): Histiocytic population was positive for CD163/CD68/p53/MYC and negative for CD34/PAX5/TdT/CD19/S100. Ki67 proliferation index is 30% in the histiocytic cells. Flow cytometry was not contributory in the evaluation of the histiocytic population and did not reveal a B-lymphoblast population.
Cytogenetics: 06/2016, 03/2017, 04/2017 (B-ALL, diagnosis, 1st recurrence and 2nd recurrence respectively): Complex karyotype with multiple clones, with loss of chromosome 17 (see PowerPoint for details).
04/2017 (histiocytic sarcoma): Unsuccessful karyotype. No chromosome 8 aneuploidy or 17p deletion by FISH.
Molecular studies: 06/2016: No t(9;22) associated with p210 or p190 BCR-ABL fusion protein.
03/2017: No t(9;22) associated with p210 or p190 BCR-ABL fusion protein.
Proposed diagnosis: Histiocytic sarcoma, arising as transdifferentiation of B-lymphoblastic leukemia
Interesting feature(s) of submitted case: This case is a rare example of transdifferentiation of B-ALL into a histiocytic neoplasm following chemotherapy. Clinical examples of such hematopoietic lineage plasticity are rare, with only a handful cases reported in the literature (PMID:20421277; PMID:21285861). In this case, the histiocytes were negative for all B-cell markers and TdT but maintained strong p53 and MYC expression, supporting their neoplastic nature and relationship to the B-ALL, with likely reprogramming and transdifferentiation of lymphoid lineage-determined blasts. It is interesting to speculate if this transdifferentiation may be related to the preceding therapy with blinotumomab (anti-CD19 “BITE” antibody); of note, several weeks later (with no additional therapy), there was no evidence of the histiocytic proliferation and the relapsed disease showed a typical B-ALL phenotype.

EAHP18-BMWS-544

Precursor B-cell acute lymphoblastic leukemia presenting with hypereosinophilia

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Case description: Previously healthy 21 year old man of Turkish origin presented with headache, back pain, mild fever, tiredness and night sweats. Peripheral blood status: WBC 193, RBC 4.6, Hgb 141, MCV 92, PLT 164. Leukocytes: neutrophils 27.9, eosinophils 141.4, basophils 1.2, lymphocytes 12, blasts 3.7, with some myelocytes and metamyelocytes.
Biopsy fixation details: Zinc formalin, formic acid decalcification
Frozen tissue available: No
Details of microscopic findings: BM clot: very small tissue fragments, 100% cellularity, increased eosinophil amount and dominance of relatively small mononuclear cells. No iron deposits or ring sideroblasts.
BM smear: 47-55% eosinophils, 19-20% blasts, underrepresented erythropoiesis (max. 7%).
PB: eosinophilia (8o% of leukocytes), max 1% blasts.
Immunophenotype: Immunohistochemistry: blasts CD34+ (90%), CD10+ (80%), MPO-, PAX5+ (50%), Tdt+ (80%), CD20-, CD79a+ (70%), p53- (10%)
Flow cytometry BM aspirate: 5-7% blasts CD45dim, CD19+, CD10++, CD38+, CD34+, HLA-DR+, CD66c+, cCD79a+, CD58+, CD22+, Tdt+, CD20-, CD5-, Ig-, CD117-, cCD3-, MPO-, CD33-
Cytogenetics: 46,(XY)
Molecular studies: BM negative for: rearrangement in CDKN2A, MLL, t(9;20), t(1;19) PBX1/TCF3, t(12;21) ETV6/RUNX1, intrachromosomal amplification of chromosome 21, t(9;22) ABL/BCR, rearrangement of FIP1L1/PDGFRA, FGFR1, PDGFRB, 4q12.
Proposed diagnosis: Precursor B-cell acute lymphoblastic leukemia presenting with hypereosinophilia.
Interesting feature(s) of submitted case: Massive eosinophilia obscuring blast increase in bone marrow. Discrepancy in blast count between flow cytometry (less than 10%), BM smears (max. 20%) and BM clot sections (almost 80%). Low blast count lymphoblastic leukemia with eosinophilia raises the suspicion of t(5;14), translocation between IL3 and IGH genes. This aberration causes hypercytokinemia and drives reactive eosinophilia. Unfortunately this analysis was not done in the patient.
The patient was treated according to NPHO protocol, with good response.

EAHP18-BMWS-548

B lymphoblastic leukemia with mature immunophenotype and MLLT3-KMT2A rearrangement

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Case description: A 7 month-old girl presented with three weeks history of loose stools, bilateral cervical lymphadenopathy, hepatomegaly, and a new onset of hypercalcemia. CBC showed: WBC 14.71 x 10^9/L, Hb 112 g/L, HCT 32.0%, RBC 4.34 x 10^{12}/L, MCV 73.7 fL, RDW 15.6%. MCH 25.8 pg, MCHC 350 g/L, and PLT 245 x 10^9/L. Leukocyte differential: Neutrophils 34.0%, immature granulocytes 4.7%, lymphocytes 35.8%, moncytes 3.8%, basophils 1.9%, eosinophils 0.0% and blasts 19.8%.
Biopsy fixation details: Formalin.
Frozen tissue available: No
Details of microscopic findings: The bone marrow was replaced by a mildly pleomorphic population of cells. Most had intermediate-sized, round-to-cleaved nuclei, dense chromatin, no nucleolus and scant blue-grey cytoplasm with perhaps a few small cytoplasmic vacuoles but no granule or Auer rod. In addition there were some cells with large, round-to-cleaved nuclei, inconspicuous nucleoli and scant blue-grey cytoplasm.
Immunophenotype: Positive for CD45 (dim, similar to granulocytes), CD19, CD20 (similar to mature B cells), sCD22, CD23, HLA-DR, and surface lambda light chain (similar to mature B cells) and negative for CD10, CD34, TdT, myeloperoxidase, CD13, CD14, CD33, CD117, CD2, cCD3, sCD3, CD4, CD5, CD7, and CD8.
Cytogenetics: 46,XX,der(2)t(2;9)(q23;p13)t(9;11)(p22;q23),der(9)t(2;9)t(9;11),der(11)t(9;11)[4]/46,XX[16]
Abnormal female karyotype with complex translocation involving chromosomes 2, 9, and 11.
Interphase and metaphase FISH analysis confirmed this complex translocation results in MLLT3-KMT2A fusion with the MLLT3-KMT2A fusions located on the derivative chromosome 2 and the derivative chromosome 11. FISH for the MYC gene region was normal
Molecular studies: None.
Proposed diagnosis: B lymphoblastic leukemia with MLLT3-KMT2A fusion.
Interesting feature(s) of submitted case:
1. True mature B cell immunophenotype (sIg+, TdT-, CD34-) is observed in less than 1% of pediatric B lymphoblastic leukemia and represents a potential diagnostic pitfall with Burkitt and other mature B cell neoplasms.
2. This patient's age, morphology, dim CD45 and absence of CD10 are all clues that this represents a B lymphoblastic process with KMT2A rearrangement rather than a mature B cell neoplasm.
References:
1. Blin N, et al. Mature B-cell acute lymphoblastic leukemia with MLL rearrangement: an uncommon and distinct subset of childhood acute leukemia. Leukemia. 2008;22:1056-59.
2. Tsao L, et al. Mature B-cell acute lymphoblastic leukemia with t(9;11) translocation: a distinct subset of B-cell acute lymphoblastic leukemia. Mod Pathol 2004;17:832-9.
3. Hilden JM, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. Blood 2006 108:441-451.

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Relapsed infantile B-lymphoblastic leukemia without B-cell lineage specific immunomarkers

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Case description: A 2 year old male presents with concern for relapsed leukemia. He presented at 6 months of age with anemia. Subsequent work-up showed B-lymphoblastic leukemia with B-ALL t(v;11q23.3);KMT2A-rearranged. Following chemotherapy, he was in remission until he presented again at 2 years of age. His diagnostic immunophenotype showed positivity for CD19, partial CD10, partial CD7, CD38, HLA-DR, and TdT. At relapse presentation, the blasts phenotype altered and while expression of CD38, CD2, CD7, and partial CD10 remained, the blasts were now negative for CD19. Additionally at this time, the blasts were also negative for TdT, cCD22, and cCD79a. He was again treated and in remission. He then received haploidentical bone marrow transplant. Six months later, he relapsed again. At second relapse he also had CNS involvement. No further treatment was available and he died 3 weeks after confirmation of second relapse.
Biopsy fixation details: Bone marrow core biopsies were obtained, fixed in B-plus and 10% formalin, and embedded in paraffin. H&E slides were prepared and marrow aspirate material was submitted for karyotype, FISH, microarray, and flow cytometry.
Frozen tissue available: n/a
Details of microscopic findings: Microscopic findings at diagnosis, first relapse and second relapse showed similar findings of a predominance of blasts that are intermediate to large in size with open chromatin, variably prominent nucleoli, and scant agranular cytoplasm. There is minimal/absent normal hematopoiesis. Remission marrows were hypocellular with maturing trilineage hematopoiesis.
Immunophenotype: At diagnosis the blasts expressed partial CD7, partial CD10, CD19, CD38, HLA-DR, and TdT. At first relapse, the blasts marked with HLA-DR, dim CD10, CD38, dim CD2, CD7, and dim CD45. They were negative for CD19, cytoplasmic CD22, cytoplasmic CD79a, CD19, TdT, cytoplasmic CD3, and myeloperoxidase. At second relapse the blasts marked with dim CD45, HLA-DR, dim CD19, partial CD2, CD7, and cytoplasmic CD79a.
Cytogenetics: At diagnosis, only FISH was performed which showed that 30% of analyzed cells had KMT2a rearrangement. Unfortunately, there were no documented cytogenetics at first relapse. During remission, karyotype and FISH for KMT2a showed normal results. Interestingly, three weeks before second relapse, chimerism showed 99% 46,XX donor. At the second relapse, karyotype showed: 46,XY,del(8)(q11.2q22),add(9)(p21),t(9;11)(p21;q23),add(17)(p11.2)[1], 46,sl,der(X)(Xpter->Xq28::11q12->11q23::9p21->9pter),der(11)(11pter->11q12::Xq28->qter)[3]/46,XX[2].
Molecular studies: n/a
Proposed diagnosis: B-lymphoblastic leukemia with t(9;11)(p21q23)
Interesting feature(s) of submitted case: The patient presented at our institution at first relapse and with minimal patient history available for review. This in conjunction with the immunophenotype (lack of B-cell specific markers) at this time could have mistakenly been interpreted as a T-lymphoblastic leukemia instead. This case highlights the importance of clinical history. While CAR T-cell therapy was not available during this child's lifetime, it would be interesting to see if CAR T-cells, which normally target CD19 B-cells, would work in this patient when the immunophenotype by flow cytometry showed negativity for CD19. Additionally, infantile B-lymphoblastic leukemias with KMT2a rearrangements are rare and at presentation often show leukocytosis and CNS involvement. The patient in this case had a white blood cell count of 6.4k/uL (hemoglobin 7.3 g/dL and platelets 57k/uL) and did not have evidence of CNS involvement until second relapse.

EAHP18-BMWS-560

B lymphoblastic leukemia with masked low hypodiploidy and TP53 mutation

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Case description: The patient is an 11 year-old male who presented with back pain and fevers. Blood counts were normal, but a spine MRI suggested a marrow-infiltrative process. Bilateral bone marrow biopsies revealed B lymphoblastic leukemia.
Biopsy fixation details: Bouin's solution
Frozen tissue available: None
Details of microscopic findings: The right core showed greater than 90% cellularity, with approximately 90% immature cells with irregular nuclear contours, dispersed chromatin, prominent nucleoli, and scant cytoplasm, consistent with lymphoblasts.
The left core showed 60% cellularity with approximately 10% lymphoblasts.
The right- and left-sided aspirate smears showed approximately 10% blasts.
Immunophenotype: Flow cytometric analysis showed 11% (left side) and 6% (right side) immature B-cells that expressed CD45 (dim), CD19 (dim), CD10 (bright), CD20 (variable),CD22, CD15 (subset), CD38, CD58, CD81, TdT, cCD79a, and HLA-DR. These cells were negative for surface immunoglobulin kappa and lambda light chains, CD34, CD56, T-cell antigens (CD2, CD3, CD5, CD7, CD4, CD8), and other myeloid antigens (CD13, CD33, CD117, MPO).
Cytogenetics: FISH was negative for BCR/ABL1 rearrangement, KMT2A rearrangement, TCF3 rearrangement, and ETV6-RUNX1 rearrangement, but did show numeric abnormalities as follows:
Four copies of ABL1 and BCR were observed in 8.0% of cells, and two copies of ABL1 and four copies of BCR were observed in 7.0% of cells.
Three copies of KMT2A were observed in 10.5% of cells, and four copies of KMT2A were observed in 14.0% of cells.
Four copies of RUNX1 were observed in 11.5% of cells.
Three copies of E2A were observed in 10.5% of cells, and four copies of E2A were observed in 15.0% of cells.
nuc ish(ASS1,ABL1,BCR)x4[16/200]/(ASS1,ABL1x2,BCRx4)[14/200],
(KMT2Ax3)[21/200]/(KMT2Ax4)[28/200],(ETV6x2,RUNX1x4)[23/200],
(E2Ax3)[21/200]/(E2Ax4)[30/200]
Karyotype showed that 5 of 20 cells were near-triploid:
69~75,XY,-X,+1,-2,-3,-4,+5,+6,-7,+8,-9,-12,+13,+19,+20,+21,+22,+mar[cp5]/46,XY[20]
Flow cytometry for ploidy assessment revealed a major hyperdiploid peak, with a very small hypodiploid peak.
Molecular studies: Sequencing: A 95-gene next generation sequencing panel performed on bone marrow from diagnosis showed a TP53 alteration in 55.9% of 435 reads: TP53 NM_000546 c.818G>A p.R273H
Follow-up sequencing of a remission peripheral blood sample showed the same TP53 alteration in 50.3% of 501 reads.
SNP array: A SNP array performed on an aspirate sample from the time of diagnosis revealed a hyperdiploid clone with relative loss of chromosomes 2,3,4,7,9 12,15,16,17,and 18, and relative gain of chromosomes 1,5,6,8,10,11,13,14,19,20,21,and 22: arr[hg19] (1,5,6,8,13,19,20,21,22)x2-4; (10,11,14)x2-3; (2,3,4,7,9,12,15,16,17,18)x2; (X,Y)x1. The low percentage of neoplastic cells precluded use of whole chromosome allele dosage patterns to definitively determine how the abnormal clone originated.
Proposed diagnosis: B-ALL with low hypodiploidy
Interesting feature(s) of submitted case: This case shows the importance of recognizing the association between B-ALL with low hypodiploidy and germline TP53 alterations. In addition, this case shows endoreduplication of the low hypodiploid clone, leading to initial ploidy and FISH results suggestive of hyperdiploidy and thus illustrating a possible diagnostic pitfall for this subtype of B-ALL. Ultimately, multiple modes of testing were necessary to reach the diagnosis.

EAHP18-BMWS-561

B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like

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Case description: The patient was 16 year old Caucasian male, previously healthy, presented with fatigue and pallor. CBC showed leukocytosis with numerous blasts, anemia and thrombocytopenia. Bone marrow exam was performed.
Biopsy fixation details: Formalin fixed clot section
Frozen tissue available: No
Details of microscopic findings: Bone marrow was hypercellular, approaching 100% cellularity, with trilineage hematopoiesis replaced by a prominent population of medium sized blasts. Bone marrow aspirate smears showed 96% blasts. Blasts were of medium size with round to oval nuclei, speckled chromatin, small nucleoli and scant agranular cytoplasm.
Immunophenotype: Flow cytometry: Blasts were positive for CD19, CD34, CD22, CD10, CD38, CRLF2 and partial TDT.
Cytogenetics: Karyotype: culture failure.
FISH: CRLF2 dual color break apart probe showed 90% nuclei with split signal.
Molecular studies: Next generation sequencing showed mutated JAK2: c.2047A>G
Proposed diagnosis: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
Interesting feature(s) of submitted case: Patient diagnosed with B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like with CRLF2 overexpression documented by flow cytometry, CRLF2 rearrangement shown by fluorescence in situ hybridization and JAK2 mutation. This case highlights utility of flow cytometry as useful screening tool in diagnosing this provisional 2016 WHO entity.

EAHP18-BMWS-569

CD19-negative B-lymphoblastic leukemia/lymphoma presented with multiple lytic bone lesions and hypercalcemia

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Case description: 22 month-old previously healthy female presented with abdominal pain, constipation, emesis, and refusing to walk. Labs: normal CBC; hypercalcemia-total Ca 17.1 mM (8.8-10.8 mM), iCa 2.52 mM (1.08-1.34 mM). X-ray: numerous subcentimeter lytic lesions in the axial and appendicular skeleton.
Biopsy fixation details: Bone marrow aspiration and biopsy were performed. Wright-Giemsa stains were performed on peripheral blood and marrow aspirate smears. Bone marrow biopsy was fixed in formalin.
Frozen tissue available: None
Details of microscopic findings: The bone marrow aspirate smears contained numerous leukemic blasts which are medium to large, with oval to convoluted nuclei, finely dispersed chromatin, and small nucleoli. Normal hematopoietic elements showed progressive multilineage hematopoiesis but are markedly reduced in numbers.
The bone marrow core biopsy consisted of trabecular and cortical bone and marrow elements largely replaced by sheets of leukemic blasts.
Immunophenotype: Flow cytometric analysis of the marrow aspirate revealed that 49% of nucleated cells were immunophenotypically abnormal B-lymphoblasts, expressing dim CD45, bright CD10 and HLA-DR, spectrum of CD34, CD38, and CD22, positive for TdT, CD79a (dim), CD24, negative for CD19, CD20, CD3, MPO, CD13, and CD33.
IHC stains of the marrow core biopsy showed that the blasts were positive for CD79a and PAX-5.
Cytogenetics: Normal female karyotype
46,XX[30]
FISH was negative for TEL/AML1 and BCR/ABL translocations, and MLL (11q23) gene rearrangements.
Molecular studies: None
Proposed diagnosis: B-lymphoblastic leukemia/lymphoma, CD19-negative
Interesting feature(s) of submitted case: Per 2016 WHO tumor classification, an acute leukemia is assigned a B-cell lineage by identification of positive CD19, and one or two (based on intensity of CD19) other positive B-cell markers including CD79a, CD10, and CD22. The peculiar feature of our case is CD19-negativity, which imposed difficulty in lineage determination, although the blasts were positive for all other three markers listed by WHO. PAX-5 immunohistochemical stain also helped to establish the lineage.
Biopsy revealed patchy distribution of blasts, which may have been missed by random biopsy. In fact, our patients had 2 previous biopsies that did not reveal blasts.
CD19-negative B-ALLs are very rare, but a case report (Sultan I, et al. Pediatric Blood Cancer 2004;43:66) showed association with lytic bone lesions and hypercalcemia, like our case.
CD19 negativity is significant for disease monitoring and treatment, as most of minimal residual disease flow cytometry protocols gate on CD19-positive population, and CAR-T cell therapy will not work on CD19-negative B-ALLs.

EAHP18-BMWS-162

TAFRO syndrome in a patient with multicentric Castleman disease (idiopathic, HHV8-negative).

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Case description: A 60 year-old-female with multi-organ failure was transferred to our institution for further workup and management. Her past medical history was insignificant. Four months prior to her visit, she had sore throat, flu-like symptoms and cough. Steroids were prescribed when she failed to respond to conservative treatment. A month later, she was admitted to a local hospital for management of pleuritic chest pain with respiratory compromise, pancytopenia, and acute kidney injury requiring hemodialysis. She was afebrile but developed significant jaundice, ascites, pleural & pericardial effusions, and peripheral edema. She required vasopressors from multiorgan failure. Labs showed high alkaline phosphatase, CRP, IL-6 (17.88 pg/mL, ref range: 0.31-5.00 pg/mL), hypergammaglobulinemia (3.4 g/dL, ref range: 0.6-1.6 g/dL) and negative for HIV, HBV, HCV, and HHV8. CT abdomen/pelvis/chest showed diffuse lymphadenopathy. Lymph node (LN) and bone marrow (BM) findings are described below. She had a prolonged hospital stay and received therapy with siltuximab, high-dose steroids and rituximab. However, she continued to deteriorate and died of multi-organ failure.
Biopsy fixation details: LN: formalin
BM: B5/decalcification
Frozen tissue available: NA
Details of microscopic findings: LN: Widely spaced, atretic follicles with regressed germinal centers and onion-skinning of mantle zone lymphocytes. The interfollicular area is expanded with sheets of plasma cells in the background of vascular proliferation.
BM: Hypercellular bone marrow with granulocytic and megakaryocytic hyperplasia and normal erythropoiesis; atypical megakaryocytes and loose megakaryocytic clusters. Increased reticulin fibrosis, grade 1 of 3.
Immunophenotype: LN: Negative for HHV8. CD21 shows loose clusters of follicular dendritic cells, and plasma cells in the interfollicular area are polytypic.
Cytogenetics: NA
Molecular studies: Negative JAK2 V617F
Proposed diagnosis: TAFRO syndrome in a patient with multicentric castleman disease (idiopathic, HHV8-negative).
Interesting feature(s) of submitted case: Here we report a rare case of HIV/HHV8-negative idiopathic Multicentric Castleman Disease (iMCD), who developed the progressive and fatal clinical syndrome of thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction and organomegaly (TAFRO). This constellation of clinical findings was first described in Japanese patients as TAFRO by Kawabata et al. [1]
This case is interesting because of its rarity, and the utility of both BM and LN biopsies in confirming the diagnosis. BM biopsy not only allows exclusion of other etiologies for the cytopenia, but is also helpful in confirming fibrosis as one of the TAFRO criteria. Overall the BM features are nonspecific, but the megakaryocyte hyperplasia with slight atypia and reticulin fibrosis, may be a pitfall and lead the pathologist to diagnose a myeloid neoplasm (as was initially suspected in this case).[2] Interestingly patients with TAFRO seem not to have the polytypic plasmacytosis which is common in BM of other iMCD patients. Lymphoid aggregates with Castleman-like features in the BM are rare and not seen in this case.
Classically, TAFRO is thought to be associated with iMCD which occurs most commonly with plasma cell (PC) variant histology. Based on the recent criteria proposed by Fajgenbaum et al, this case meets criteria for PC variant, albeit with some hyaline vascular (HV) features as well.[3] More recent studies of well-documented TAFRO cases have found that they have fewer plasma cells than other cases of iMCD suggesting a more mixed (HV/PC) histology. Cases with HV morphology have also been reported.

EAHP18-BMWS-270

Copy number loss of 15q26 in CD3-CD4+ T-cells of lymphocytic variant of hypereosinophilic syndrome

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Case description: The patient is a 21-year-old male with a history of eosinophilia of uncertain etiology since age 8. He initially presented with intermittent vomiting, facial swelling, rash, and eosinophilia (absolute count up to 12.0 K/µL). He has never had lymphadenopathy or hepatosplenomegaly. He previously underwent work up that was significant only for intermittently positive T-cell gene rearrangement studies on bone marrow. He has been treated for years with oral steroids and imatinib with improvement in symptoms and eosinophil count. Separate trials to wean both imatinib and steroids led to worsening eosinophilia. Recently he presented to our institution with 3-months of nausea, fatigue and myalgia. A bone marrow biopsy was performed.
Biopsy fixation details: Right posterior iliac crest bone marrow biopsy (decalcified, formalin-fixed) and aspirate were obtained.
Frozen tissue available: No
Details of microscopic findings: Bone marrow biopsy and aspirate were hypocellular for age (50% cellarity) with mildly increased eosinophils (8% by aspirate differential count). Unremarkable maturing trilineage hematopoiesis was seen with no increased blasts or atypical lymphoid infiltrate. CBC and peripheral blood smear were unremarkable with normal absolute (0.4 K/µL) and relative (5.2%) eosinophil counts.
Immunophenotype: Flow cytometric immunophenotyping of the marrow and peripheral blood showed a small abnormal mature T-cell population with lack of surface CD3, bright CD5, partial CD7, normal CD2 and CD4, and no CD8, CD56 or CD25 expression. The population comprised 0.29% and 0.61% of the white cells in the marrow and blood, respectively. No abnormal mature B-cell, myeloid blast, monocyte or maturing myeloid populations were identified. Immunohistochemical staining of the biopsy showed a minute aggregate of CD5(+), CD3(-) cells, consistent with abnormal T-cells.
Cytogenetics: Karyotype was normal. FISH was negative for rearrangements of PDGFRA, PDGFRB, MLL, and EVI1, deletion/loss of chromosomes 5, 7, 17 and 20q, or gain of chromosome 8.
Molecular studies: An RNA-based targeted sequencing assay that detects gene fusions among a 199-gene panel (includes PDGFRA, PDGFRB, FGFR1, JAK2, BCR, and ABL1) was negative. The abnormal T-cell and eosinophil populations were sorted by flow cytometry and tested separately by hybridization capture-based next generation sequencing that evaluates 400 genes. The T-cells showed a copy number loss of chromosome 15q26.1 (contains IDH2, BLM, and FURIN genes). The eosinophils showed no abnormalities. T-cell gene rearrangement studies on the marrow did not detect clonal rearrangement in the minute cell population (outside testing of multiple prior bone marrow biopsies showed clonal rearrangements of TCR beta and gamma).
Proposed diagnosis: Lymphocytic variant of hypereosinophilic syndrome
Interesting feature(s) of submitted case: Lymphocytic variant of hypereosinophilic syndrome (LV-HES) is a rare type of HES where abnormal T-cells overproduce T helper (Th2) cytokines causing eosinophil overgrowth[1]. Few cases are reported in the literature. Genetic aberrations remain elusive. Del(6q) was described in two cases and STAT3 mutation in one[2,3]. Using flow cytometric cell sorting, we confirmed 15q26 copy number loss in the abnormal T-cells only, supporting this as a T-cell driven process with reactive eosinophilia. Since the T-cells have abnormal immunophenotypes and often show clonal TCR gene rearrangements, it has been proposed that LV-HES is a type of indolent T-cell lymphoproliferative disorder. However, LV-HES rarely progresses to T-cell lymphoma (WX unpublished data). Thus, it is crucial not to misdiagnose or treat it as such.

EAHP18-BMWS-372

38 year-old man with severe anemia, marrow fibrosis, and lymphoplasmacytic infiltrate

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Case description: The patient developed severe anemia in 2015 (Hgb 5g/dl), and was diagnosed with aplastic anemia. He received steroid, ATG and cyclosporin A, however, hemoglobin level did not improve. He was referred to our institution in November 2016.He was RBC transfusion dependent, and was not on specific therapy. CBC showed severe anemia and mild thrombocytopenia (WBC 4900/ul, Hgb 5.8 g/dL, MCV 90 fL, Plt 85000/ul, neutro 58.9%, lymph 37.0%, mono 3.5%, eosino 0.4%, baso 0.2%). LDH was normal (128 U/L; Ref 120-246). Total bilirubin, vitamin B12, folate, iron, ferritin, haptoglobin were all normal. He had no significant past medical history or history of toxin or chemical exposure. Radiology exam did not show lymphadenopathy or hepatosplenomegaly.
Biopsy fixation details: 10% formalin
Frozen tissue available: No
Details of microscopic findings: Bone marrow biopsy: Erythroid predominant trilineage hematopoiesis with marked myelofibrosis and lymphoplasmacytic infiltrate. Dysmegakaryopoiesis and osteosclerosis are not evident.
Peripheral blood smear: Few circulating myelocytes. No circulating blasts. No dysgranulopoiesis. Large granular lymphocytes are increased. Tear drop cells and nucleated RBCs are rare.
Immunophenotype: CD138, kappa, and lambda light chain stains highlight increased polytypic plasma cells. CD3, CD4, and CD8 highlight increased interstitial lymphocytes. CD71 highlights increased erythroid precursors. CD34 shows no increase in blasts. CD117 highlights scattered mast cells. Myeloperoxidase highlights myeloid population. CD61 highlights megakaryocytes. CD20 highlights scattered B-cells. HHV8, IgG4, and pan-cytokeratin are negative.
Flow cytometry showed no PNH clone on red cells, granulocytes, or monocytes.
Atypical NK cell with CD5 expression was detected (2.5% of WBC).
Cytogenetics: 46, XY[18]. FISH for chromosome 5, 7, 8 show no abnormality. DEB assay is negative
Molecular studies: No evidence of mutation in tested genes
(ABL1, ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CBLC, CDKN2A, CEBPA, CSF3R, CUX1, DNMT3A, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, HRAS, IDH1, IDH2, IKZF1, JAK1, JAK2, JAK3, KDM6A, KIT, KRAS, MAP2K1, MLL, MPL, MYD88, NOTCH1, NPM1, NRAS, PDGFRA, PHF6, PML, PTEN, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, SUZ12, TET1, TET2, TET3, TP53, TYK2, U2AF1, WT1 and ZRSR2)
T-cell receptor monoclonal rearrangement: not detected.
Proposed diagnosis: Primary autoimmune myelofibrosis
Interesting feature(s) of submitted case: Findings commonly seen in primary myelofibrosis were not observed. Cytogenetic and molecular studies did not detect clonal hematopoiesis. Because steroid, ATG and cyclosporin A did not improve his anemia, treatment with anti-CD38 (daratumumab) was attempted. His hemoglobin level improved up to 10g/dL, and he became transfusion independent for 10 months. However, he again gradually became anemic, and this time, he presented with pancytopenia. Bone marrow biopsy obtained in November 2017 showed virtually acellular marrow, and myelofibrosis was not observed. The etiology of aplastic marrow is unclear; this could represent progression of underlying marrow failure syndrome. Although bone marrow failure related to daratumumab has not been reported so far, anti-CD38 could have targeted CD38 positive stem cell niche in this case. He received allogeneic stem cell transplant in December 2017, and is currently showing excellent recovery.

EAHP18-BMWS-373

Lymphoproliferative disorder associated with STAT3 gain-of–function germline mutation

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Case description: A 45-year-old female initially presented with recurrent fatigue and 10 pounds weight loss. She was found to have cytopenias, hypogammaglobulinemia, splenomegaly and hypermetabolic lymphadenopathy. Her past medical history was significant for recurrent otitis media in childhood, Streptococcal pharyngitis and sinusitis. She was also found to have a short stature in her childhood. Her daughter has similarly severe growth failure and developed autoimmune hepatitis requiring liver transplantation. The patient underwent left inguinal lymph node excisional biopsy and bone marrow core biopsy.
Biopsy fixation details: A bone marrow biopsy and aspirate are obtained from the posterior iliac crest. The clot section and core biopsy are fixed in B plus Fix (BBC) fixative. The core biopsy is decalcified in Formical (formic acid, formaldehyde and EDTA) before processing and embedding in paraffin.
Frozen tissue available: No.
Details of microscopic findings: The bone marrow core biopsy shows an 80% cellular marrow with nodular and interstitial lymphoid cell infiltrate. There is a predominance of erythroid component (M:E ratio 0.6), and mild reticulin fibrosis. The lymphocytes are predominantly small. Blasts are not increased. Megakaryocytes, myeloid precursors show unremarkable morphology.
She also underwent left inguinal lymph node excisional biopsy which showed preservation of the normal architecture and sinuses histiocytosis.
Immunophenotype: By immunohistochemical stain on the bone marrow core biopsy, there are approximately 10-15% B cells (with nodular distribution) and 30% T cells (predominantly interstitial distribution, focally vaguely nodular). Flow cytometry detected a CD5-/CD10-, lambda light chain restricted B cell population (12% of the total events), T cell population (15.5% of the total events) with an inverted CD4:CD8 ratio of 0.34, and a small population of CD4-/CD8- gamma-delta T cells (1.79% of the total events).
Flow cytometry performed on the lymph node also showed a CD5-/CD10-, lambda restricted B cell population. This population comprised 20% of the total events.
Cytogenetics: Normal female karyotype (46,XX[20]).
Molecular studies: Whole exome sequencing revealed a STAT3 gain-of-function mutation (c.521 T>C, p.F174S). T cell and B cell gene rearrangement studies on the bone marrow identified clonal immunoglobulin heavy (IGH) and kappa light chain (IGK) gene rearrangements, and clonal TCR beta and gamma receptor gene rearrangements.
Proposed diagnosis: Lymphoproliferative disorder associated with germline gain-of-function STAT3 gene mutation
Interesting feature(s) of submitted case: The patient with presentation of recurrent infection and weight loss was clinically found to have cytopenias, hypermetabolic lymphadenopathy, splenomegaly, decreased CD4+ T cell count and hypogammaglobulinemia. Lymphoproliferation was revealed in lymph node and bone marrow biopsies, including monotypic B cell population and atypical T cell populations. There was no evidence of overt T-cell large granular lymphocyte leukemia. No definitive diagnosis of B- or T-cell lymphoma can be rendered. The above clinical and pathological findings are associated with the patient's germline gain-of-function mutation of STAT3 gene. Lymphadenopathy, autoimmune cytopenias, multiorgan autoimmunity, infections, short stature, and positive family history are the clinical features of this recently described disease [1, 2].
1. Milner JD, et al. Blood. 2015 Jan 22;125(4):591-9.
2. Flanagan SE, et al. Nat Genet. 2014 Aug;46(8):812-814.

EAHP18-BMWS-388

Non-neoplastic lymphoid proliferation in an elderly woman with secondary autoimmune myelofibrosis

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Case description:
A 76-year-old Hispanic woman presented with pancytopenia. She had type II diabetes mellitus, hypertension, and history of autoimmune hemolytic anemia (AIHA). She complained of fever, chills, and sore throat, while on cyclosporine and following the completion of dexamethasone therapy for AIHA. The patient had borderline splenomegaly attributed to AIHA. A bone marrow biopsy was performed to assess for the cause of her cytopenias.
Biopsy fixation details: Biopsy was placed in B5 fixative for 2 hours and decalcified prior to processing.
Frozen tissue available: No
Details of microscopic findings:
The peripheral blood smear showed a marked normochromic, normocytic anemia, absolute neutropenia, and mild thrombocytopenia. Large granular lymphocytes were relatively increased. No dysplasia, eosinophilia, basophilia, or increase in blasts was seen.
No bone marrow aspirate was obtained due to a dry tap. The trephine biopsy was moderately to markedly hypercellular (ranging from 80 to 100% cellularity) with marked erythroid and megakaryocytic hyperplasias. Megakaryocytes showed a spectrum of morphology from small to large forms, and occasional bare ('naked') nuclei were seen, however, significant megakaryocytic atypia was not observed.
Multiple small to medium-sized, nonparatrabecular lymphoid aggregates were present. composed of cytologically bland lymphocytes. Reticulin staining highlighted a diffuse and dense, mild to moderate increase in reticulin fibrosis with extensive intersections (MF grade 1-2/3).
Immunophenotype:
Flow cytometry showed no diagnostic immunophenotypic abnormalities: B-cells showed polytypic surface light chain expression; T-cells had no overt pan T-cell aberrancies and no significant increase in large granular lymphocytes.
Immunohistochemical stains (IHC) highlighted multiple small to medium-sized, nonparatrabecular, generally well-circumscribed lymphoid aggregates, which were B-cell predominant. In addition, CD8+ T-cells were also increased with mostly interstitial distribution, though rare intrasinusoidal CD8+ cells were noted. CD57 and TIA-1 were positive only in a minor subset of interstitially scattered cells.
Cytogenetics: Not performed.
Molecular studies: PCR studies for T-cell receptor gene rearrangements were negative.
Proposed diagnosis: Autoimmune myelofibrosis (AIMF) in the setting of AIHA
Interesting feature(s) of submitted case:
AIMF is an under-recognized entity, requiring careful correlation of pertinent clinical and laboratory data with morphologic findings. When received in consultation, AIMF cases have sometimes been misclassified as MDS, MPN, or lymphoma. Interesting features in this case are the multiple B-cell predominant lymphoid aggregates, which have been reported in only a minor subset of AIMF cases (<5%). On the other hand, the B-lymphoid aggregates showed otherwise benign features (e.g. bland cytology, absence of infiltrative borders, small to medium size) and B-cells were polytypic on flow cytometric analysis. The presence of borderline splenomegaly, neutropenia, and rare intrasinusoidal CD8+ T-cells briefly raised the possibility of T-LGL leukemia; however, no abnormal population was detected by IHC or flow cytometry and clonality was not detected by PCR for T-cell receptor gene rearrangements. This case also illustrates a greater degree of bone marrow fibrosis than is typically seen in AIMF cases, with MF grade 2 seen in about 10% of cases in a study of 29 patients. This patient has demonstrated no evidence of malignancy after 5 years of clinical follow-up.

EAHP18-BMWS-409

Myeloid neoplasm with 10-15% blasts and atypical plasmacytoid dendritic cell proliferation

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Case description: We present the bone marrow biopsy from a 54 year old man with anemia, splenomegaly, and peripheral monocytosis. Aspirate smears show a myeloid neoplasm with 10-15% blasts, megakaryocytic dypslasia, and erythroid dysplasia. The marrow clot and core sections demonstrate compact, dense aggregates of plasmacytoid dendritic cells (PDC). The PDCs express CD123 and CD4 along with aberrant CD5 and CD10, supporting their neoplastic nature. We also considered the possibility of blastic plasmacytoid dendritic dell neoplasm (BPDCN). However, no expression of CD56 or TdT is seen in the PDCs and the Ki-67 is less than 10%. We also questioned whether the plasmacytoid cells may be in fact be the patient's blasts with expression of multiple aberrant markers. However, CD117, CD34, and CD33, which are expressed on the patient's blasts by flow, are negative by immunohistochemistry in the PDC aggregates.
Biopsy fixation details: The bone marrow biopsy was decalcified and fixed in formalin.
Frozen tissue available: No frozen tissue was submitted.
Details of microscopic findings: Aspirate smears demonstrate adequate cellular spicules with mild erythroid dysplasia, including nuclear blebbing and irregular nuclear contours, in greater than 10% of cells. Myeloid cells are left-shifted and show 10.5% blasts on a 500 cell manual differential. Megakaryocytes are dyplastic with numerous hypolobated and micromegakaryocyte forms and separation of nuclear lobes. The bone marrow biopsy sections are hypercellular for age (90%). Erythroid cells are decreased in number with irregular forms. Myeloid cells are increased in number with left-shifted maturation. The M:E ratio is 2:1. Megakaryocytes are increased in number and include hypolobated and micromegakaryocyte forms. Blasts are increased and scattered throughout the interstitium with focal clustering. Multiple well-circumscribed aggregates of mononuclear cells are noted with intermediate-size round nuclei, dispersed chromatin, slight nuclear indentations, pinpoint nucleoli, and moderate amounts of pink cytoplasm. Few admixed small, heterogeneous lymphocytes are seen.
Immunophenotype: Immunostains show the mononuclear cells express CD123 and CD4 with coexpression of aberrant CD5 and CD10. BCL2 is present on a minor subset of the cells. S-100 focally stains dendritic cell processes in the area of the aggregate. TCL1, CD56, TdT, mast cell tryptase, CD33, CD34, CD117, lysozyme, PAX5, and CD163 are all negative in the mononuclear cells. Ki-67 shows a proliferation index of <10% in the mononuclear cell aggregates and 50% in the background myeloid neoplasm. CD34 stains approximately 15% blasts in the background marrow.
Cytogenetics: Cyogenetics shows deletion of 7q in 8 cells and the remaining 10 cells show a normal male karyotype.
Molecular studies: No molecular studies were performed.
Proposed diagnosis: Myeloid neoplasm with 10-15% blasts and associated atypical plasmacytoid dendritic cell neoplasm
Interesting feature(s) of submitted case: PDCs have been shown to be "tumor forming" in the setting of myeloid neoplasms, particularly CMML and myeloid neoplasms with monocytic differentiation, and may accumulate in bone marrow, skin, lymph node, and spleen. In one study, the majority of cases lacked TCL1. Aberrant expression of CD2, CD5, CD7, CD10, CD14, or CD15 may support that the PDCs are neoplastic. Furthermore, multiple FISH studies have shown that that these PDCs have the same chromosomal alterations as the associated myeloid neoplasm. While these collections of PDCs behave more indolently that BPDCN, prognosis in these cases is generally related to the progression of the underlying myeloid neoplasm.

EAHP18-BMWS-478

Gelatinous transformation of bone marrow: lymphoma, carcinoma or both?

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Case description: This case describes a 78-year-old man, presenting with pancytopenia, who had gelatinous transformation of the marrow and a small CD5-negative CD10-negative clonal B-cell population on flow cytometry. His clinical course deteriorated with the development of polyserositis and precipitating platelet counts with gastrointestinal haemorrhage despite steroids, transfusions and rituximab. Multiple investigations failed to detect the T3 adenocarcinoma in the sigmoid colon until his autopsy.
Biopsy fixation details: 10% formalin
Frozen tissue available: No
Details of microscopic findings: Hypocellular marrow with tri-lineage erythropoiesis, gelatinous transformation and occasional reactive-looking small lymphoid follicles
Immunophenotype: CD20 and CD3 revealed normal compartmentalisation of B-cells and T-cells in the follicles but no B-NHL in the background marrow
Cytogenetics: None performed
Molecular studies: MYD88 L265P; negative
Proposed diagnosis: Gelatinous transformation of bone marrow with a small clonal B-cell population of non-CLL phenotype and a sigmoid colon adenocarcinoma but no nodal or extranodal lymphoma.
Interesting feature(s) of submitted case: The minimal marrow lymphoid infiltration does not explain the sustained low platelet counts.

EAHP18-BMWS-490

TFH hyperplasia of uncertained significiance

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Case description: Sixty-years-old caucasian woman, without medical history, wich consult for a chronic dry cough.
Biological investigations reveal anemia (11.5g/L) and a positive EBV serology (4.5log, IgG+, IgM-), in favor of an old infection.
CT scann show a small hepatosplenomegaly and a peribronchovascular thickening in favor of infectious sequelae.
Cytological and immunophenotyping studies of peripheral blood showed atypical monotypic kappa lymphoid B cells, with a monocytoid aspect (12% of the lymphocytes) and a Matutes score at 1/5 (CD5-/CD23+/CD43+weak/CD10-/CD38-). The myelogram found an infiltration above 0.1% of the sample by the CD5-/CD10- monotypic lymphoid B population by flow cytometry without T cell phenotypic abnormality and without cytogenetic abnormality.
Biopsy fixation details: 4% buffered formol, decalcified by EDTA and embedded in paraffin
Frozen tissue available: No
Details of microscopic findings: The biopsy measured 20 mm, and was analysable on almost all of its surface, the cellularity was homogeneous and above 40% of the medullary surface. There was no obvious abnormality of hematopoietic lines, which appear to be represented at all stages of maturation and balanced distribution.
There was a nodular lymphoid infiltration with voluminous nodules of small, irregular atypical lymphocytes associated with some slightly epithelioid cells clusters. The infiltration represents at least 30% of the medullary elements.
Atypical cells such as Hodgkin cells are not seen.
Immunophenotype: The immunohistochemical study carried out shows that this nodular lymphocyte infiltration is formed of CD3+, CD4+, CD2+, CD7+, CD5+, TFH T cells associated with rare B cells (some of them which correspond to the overexpressing EBER RNA cell by in situ hybridization technique).
CD4 T cells express PD1, sometimes CXCL13, but do not express BCL6 or CD10. There is no monotypy with kappa and lambda light chains. There are rare CD8 cells mixed with the CD4 cells. We also recognize some rare CD30 cells. There was no labeling with cytotoxic markers such as perforin, granzyme, or TIA1.
Cytogenetics: The bone marrow caryotype was normal (46XX[20]).
Molecular studies: A study of lymphocyte clonality was performed by PCR on the paraffin embedded tissue sections, (with Biomed 2 recommendations) and showed no monoclonal T proliferation but highlights a monoclonal B proliferation.
Proposed diagnosis: Nodular and interstitial T lymphocyte infiltration of CD4+ phenotype without T clonality can be either an infiltration by TFH-cell T lymphoma (angioimmunoblastic T cell lymphoma) or a reactional hyperplasia TFH cells, either in an infectious context or an auto immune disease or associated to a marginal zone lymphoma.
Interesting feature(s) of submitted case: This case ask the question of the diffential diagnosis of a TFH hyperplasia in the bone marrow.
First of all, between an angioimmunoblastic T-cell lymphoma (whose T-cell receptor genes show clonal rearrangements in only 75-90% of cases) or a reactional hyperplasia TFH cells.
Second of all, it ask the causes of a TFH hyperplasia in the bone marrow. TFH hyperplasia in bone marrow or in blood can be seen in some infections or in auto immune diseases (like lupus), playing an important role in promoting pathogenic autoantibody production.
In this case, due to the little blood infiltration by a B monotypic population associated to a monoclonal B proliferation in the bone marrow, we can also discuss the association between a marginal zone lymphoma and a bone marrow TFH hyperplasia.

EAHP18-BMWS-494

Multicentric Castleman disease involving the bone marrow associated with features of POEMS

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Case description: 23 year-old Black male with a history of "tumid lupus" (diagnosed in 2012 at an outside institution and untreated due to incompliance) presented to the UAB in July, 2017 with an approximately 6 month history of worsening pain in the ankles, knees, and wrists, swelling and numbness. He also had unintentional weight loss (from 400 lbs to 240 lbs in few months) along with loss of appetite. Over the past 2 weeks, he developed a nighttime cough, shortness of breath, fever and chills.
On physical exam, he had scattered subcutaneous nodules. The lab testing showed anemia (Hgb: 7.3 g/dL, MCV: 88 fL) and ESR of 41. The remaining CBC and basic metabolic panel values were normal. Anti-DNA, ANA, anti-CCP and RF levels were within normal limits. Serum IgG level was increased (2362 mg/dL). **IL-6 level was high (719 Hf)**. Imaging showed diffuse cutaneous thickening, multiple subcutaneous nodules, bilateral inguinal, external iliac, axillary, supraclavicular and mediastinal lymphadenopathy, pleural effusion and patchy sclerosis in bilateral femoral heads. A skin biopsy showed slight acanthosis and pigment incontinence. A subsequent left inguinal lymph node excision and bone marrow biopsy were performed.
Biopsy fixation details: A portion of the lymph node was submitted for flow cytometry. The remaining lymph node and bone marrow biopsies were fixed in buffered 10% formalin for at least 6 hours. Brief decalcification of bone marrow was performed. 4-5 µ sections were obtained.
Frozen tissue available: N/A
Details of microscopic findings: The left inguinal lymph node excisional biopsy displayed prominent follicular hyperplasia and increased numbers of interfollicular plasma cells forming clusters. The follicles were significant for partial regression, hyalinized germinal centers and mantle zones with "onion skinning" in some of them and hyalinized blood vessels some of which penetrating into the follicles.
The bone marrow biopsy was significant for a marked lymphoplasmacytic infiltrate thickened and hyalinized blood vessels in the background of 70% cellular marrow. A benign lymphoid follicle was surrounded by plasma cells. Congo red did not show amyloid and Elastic stain highlighted hyalinized blood vessels .
Immunophenotype: Flow cytometric analysis on both lymph node and marrow showed no evidence of a clonal plasma cell, B- or aberrant T-cell populations. HHV8 immunohistochemical stain was negative in both samples.
Cytogenetics: 46,XY[20].
Molecular studies: PCR for HHV8 DNA was negative. FISH for myeloma was negative.
Proposed diagnosis: HHV8- Multicentric Castleman (MCD) disease with features of POEMS syndrome.
Interesting feature(s) of submitted case: Morphologic subtypes CD includes haline vascular, plasma cell and mixed types. The disease can be unicentric or multicentric with or without HHV 8 infection. The syndrome of TAFRO (thrombocytopenia, ascites/anasarca, myelofibrosis/fever, renal dysfunction/reticulin fibrosis and organomegaly) is a recently described variant of HHV8- MCD. Our case does not meet the diagnostic criteria for this variant. Our patient had a diagnosis of "tumid lupus" which is in differential diagnosis of MCD. This diagnosis was excluded based on the clinical and laboratory findings.
Interestingly, our case had features that can be seen POEMS syndrome including neuropathy, sclerotic bone lesions, edema, and pigmentary skin changes. However, it lacked the monoclonal plasma cell proliferation which is required for diagnosis of POEMS syndrome.

BONE MARROW WORKSHOP SESSION 2

T-NHL and Hodgkin Lymphoma

Chairs: A. Attygalle, C. Laurent

EAHP18-BMWS-102

Primary bone marrow Anaplastic Large Cell Lymphoma, ALK negative and reactive haemophagocytic syndrome

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Case description: 52 year old male presented with one month history of fevers, sweats, progressive pancytopenia, raised LDH and ferritin and abnormal LFTs. CT scan showed no lymphadenopathy or hepatosplenomegaly. Bone marrow examination revealed involvement by ALCL, ALK negative and haemophagocytosis.
Biopsy fixation details: Fixation – Formalin for 24 hrs Decalcification – 10% Formic Acid for 6 hrs
Frozen tissue available: not available
Details of microscopic findings: BONE MARROW ASPIRATE:There is a population of atypical cells with size ranging from medium though large and very large. The largest forms have a sizecomparable with the size of a small megakaryocyte. They have a deeply basophilic cytoplasm, at times containing azurophilic granules. Nucleiare pleomorphic, some are round and some are irregular. Bi- and multinucleated/multilobulated forms are also seen. Majority containmultiple basophilic nucleoli. Mitotic figures are also seen.Haemophagocytic macrophages are frequently seen.BONE MARROW TREPHINE: There is a marked interstitial increase in lymphoid cells. The majority are small to medium lymphocytes, but a clear population of largeand very large atypical cells is also present. The latter are scattered singly in the interstitium and among the smaller lymphoid cells. In areas ill defined lymphoid aggregates containing both small and large cells are present. The large cells are pleomorphic with irregular nucleithat are often multi-lobulated, multinucleated and hyperchromatic, containing multiple prominent nucleoli. Hallmark cells are also seen.Mitotic large cells are present. The largest lymphoid cells are at times difficult to distinguish from the megakaryocytes.Haemophagocytic histiocytes are often seen.Reticulin: Increased (MF-2).CD45: Most of the large cells are positive with fewer negative forms.CD3: A number of the large lymphoid cells show a weak cytoplasmic positivity.CD2: The large cells display both membranous and Golgi positivity.CD5: fewer large cells are positive.CD4: the large cells are negative.Granzyme B: Strongly positive in the large cells.CD30: The medium and large cells are positive with accentuation in the membrane and Golgi regions.
EMA: Positive in a proportion of the large cells.PD-1: Many of the smaller lymphocytes are positive. The large cells are negative.CD68: Many positive cells.The large cells are negative for: CD56, ALK-1, EBER-ISH, Pan CK, AE1/3, CD20, MUM-1, CD7, PAX-5, CD138, S-100, CD15, CD23, CD21, CD10, CyclinD1, CD1A.
CD61 and FVIII-ra: many megakaryocytes, in many areas these are seen scattered between the lymphoma cells
Immunophenotype: Flow cytometry: The lymhpoid cells have low forward scatter consistent with small lymphocytes. They are predominantly CD4 or CD8 positive T lymphocytes with no oss of or aberrant antigen expression. B lymphocytes are scantyand are polyclonal.The findings are consistent with a reactive lymphoid population.
Cytogenetics: Karyotype and FISH were not performed at initial diagnosis. Karyotype was carried out at disease relapse (4 month after 1st diagnosis) with the following results:
Karyotype: 85~91,XXYY,+X,+X,-Y,-Y,+der(2)t(2;18)(q35;q23),t(2;18)(q35;q23)x2,add(3)(q?25)x2,-4,-7,-9,-9,-10,+13,-14,-15,-15,+18,+18,-22,+mar[cp11]/46,XY[19]
Molecular studies: not performed
Proposed diagnosis: Anaplastic Large Cell Lymphoma ALK-negative.Secondary Haemophagocytic Lymphohistiocytosis (HLH)
Interesting feature(s) of submitted case: Anaplastic large cell lymphoma ALK negative with primary bone marrow presentation and associated Haemophagocytic Lymphohistiocytosis (HLH)

EAHP18-BMWS-217

Aggressive cytotoxic T-cell lymphoma following successful therapy of CLL.

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Case description: M, born in 1953. CLL diagnosed in 2000 in another institution; history of relapses and several lines of treatment. Prior to the submitted biopsy (Dec. 2014) completed Bendamustine-Rituximab, at the time of the biopsy was on Idelalisib/placebo maintenance study in the Idelalisib arm. Response recorded as excellent, but remained anaemic (Hb 96g/L) and thrombocytopenic (plt ~50x10^9/L). ~1% CLL MRD on BM flow cytometry, nothing sinister detected on the last BM aspirate. Reported new right shoulder pain; imaging showed skeletal lesions. Decision to palliate following the new diagnosis (see below); died shortly thereafter.
Biopsy fixation details: Processed according to the Hammersmith Protocol [JCP 2006;59:903]
Frozen tissue available: No
Details of microscopic findings: Two topographically distinct and morphologically different types of lymphoid infiltrates:
[1] Scattered large/monstrous T-cells, often with frankly anaplastic or HRS-like morphology, in a fibrotic dense background rich in histiocytes and small T cells. These infiltrates, representing peripheral T-cell lymphoma of cytotoxic origin, occupy ~2/3 of the sample.
[2] Conventional CLL infiltrates, organised in a few partly confluent nodules seen at the tip of the biopsy.
Immunophenotype: [1] PTCL: CD3+, CD2+/-, CD4-, CD8+, Granzyme B+/-, CD5-, CD7-, CD43-, PD1-, CD25-, CD56-, CD57-, CD30-, ALK1-, CD15-, Fascin-, LCA-, CD20-, PAX5-, CD79a-, CD10-, BCL6-, MUM1-/+, CK-, S100-, P53-, Cyclin D1-, EBER-, ki67+.
[2] CLL: expected immunophenotype (CD20+, CD5+), negative P53.
Cytogenetics: Not done
Molecular studies: Not done on this material.
CLL (examined in 2013): P53: no deletion, ATM: 40% deleted
Proposed diagnosis: AGGRESSIVE PERIPHERAL T-CELL LYMPHOMA WITH CYTOTOXIC IMMUNOPHENOTYPE DEVELOPING IN A PATIENT WITH LONG-LASTING CHRONIC LYMPHOCYTIC LEUKAEMIA.
Interesting feature(s) of submitted case: Although on the routine stains the morphology of the high-grade lymphoma is strongly suggestive of Richter's syndrome, in particular of the Hodgkin-type, its immunophenotype indicates a peripheral T-cell lymphoma of cytotoxic origin. There is some literature suggestive of increased risk of T-cell lymphoma development in patients with CLL (Am J Surg Pathol 2014;38:279, Am J Surg Pathol 2004;28:849, Int J Dermatol 2014;53:966) and interestingly, non-cutaneous PTCL seen in this context very frequently show a cytotoxic immunophenotype. Development of these tumours may be related to altered immunity status of CLL patients, whose cytotoxic cells may be over-stimulated and prone for clonal evolution. Some reported patients were never treated for their CLL. Thus, strictly speaking, these are neither examples of Richter's syndrome nor secondary therapy-related cancers. Behaviour of systemic cytotoxic T-cell lymphomas in CLL patients seems to be very aggressive.
Anaplastic/Hodgkin/Reed-Sternberg-like morphology of the tumour, not associated with 'anaplastic' immunophenotype (negative CD30, CD43, Fascin and ALK1; mostly negative MUM1) is a unique and probably not reported feature of the present case.

EAHP18-BMWS-284

EBV Negative Aggressive NK-Cell Leukemia with Bone Marrow Presentation.

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Case description: 52-year-old man with history of testicular seminoma managed with surgical resection August 2016. A followup CT chest/abdomen/pelvis performed December 2016 was within normal limits with no evidence of lymphadenopathy. In April 2017 he noted new onset of fevers, night sweats, fatigue, intermittent left upper quadrant abdominal pain, and bilateral cervical lymphadenopathy. His CBC from 5/8/17 showed marked leukocytosis (66.7 K/uL) and thrombocytopenia. His LDH level was markedly elevated (2241 U/L). A chest x-ray showed small bilateral pleural effusions. No skin lesions were noted. A PET/CT of chest/abdomen/pelvis on 5/11/17 showed widespread lymphadenopathy with increased FDG uptake (up to 9.6), hepatomegaly, splenomegaly, as well as diffusely increased FDG activity of the bones. A bone marrow biopsy was performed. Following the diagnosis, the patient was treated with SMILE chemotherapy and had a negative bone marrow in July 2017. However, a month later he presented with CNS involvement with positive CSF cytology. Despite further salvage therapy, he continued to deteriorate with neurological deficits, and expired in October 2017.
Biopsy fixation details: B5/decalcification.
Frozen tissue available: None.
Details of microscopic findings: CBC (5/9/17): Hgb 11.6 g/dL; RBC 3.83x10(12)/L; MCV 90.1 fL; RDW 18.8%; WBC 51.6 x10(9)/L; PLT 80 x10(9)/L. Differential (%): neutrophils 6; lymphocytes 92; monocytes 2; nRBCs 1. The peripheral blood smear showed marked lymphocytosis with predominance of intermediate sized lymphocytes with irregular nuclei, coarse chromatin, variably prominent nucleoli, and abundant finely granulated cytoplasm. The bone marrow aspirate and core biopsy were markedly hypercellular (90% cellularity), and showed extensive involvement (80% of marrow cellularity) by an abnormal interstitial infiltrate of intermediate-sized cells morphologically similar to those in the peripheral blood. Granulopoiesis and erythropoiesis are markedly diminished. Adequate megakaryocytes are present.
Immunophenotype: Flow cytometry (peripheral blood): Phenotypically abnormal NK-cell population detected (95% gated lymphoid events; 78% total analyzed events), which express CD2, CD16 (dim), CD26, CD56, CD94 (uniform), and NKG2a (uniform); and do not express sCD3, CD4, CD5, CD7, CD8, TCR-gamma/delta, CD57, or KIR antigens (CD158a, CD158b, CD158e). Blasts are not increased. No monotypic B-cell population.
Immunohistochemistry: Positive for CD2, CD3, and CD56; negative for CD5 and CD7.
In situ hybridization for Epstein-Barr virus encoded RNA (EBER): Negative.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Aggressive NK-cell leukemia, EBV negative.
Interesting feature(s) of submitted case: This case illustrates the typical presentation (including leukemic blood picture, extensive bone marrow involvement, hepatosplenomegaly, high LDH, and B symptoms) and fulminant clinical course of aggressive NK-cell leukemia. An interesting feature of this case is the lack of EBV association as demonstrated by EBER. Although aggressive NK cell leukemia is almost always associated with EBV, rare EBV negative cases have been described, which appears to be for the most part clinically and pathologically similar to EBV positive cases with equally aggressive clinical course (Am J Surg Pathol 2017;41:67-74).

EAHP18-BMWS-289

Hodgkin's Lymphoma with primary presentation as pancytopenia and marrow involvement

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Case description: 27-year-old male came with progressive weakness and fever since three months. Boy was a computer assistant and could not walk a pair of stairs. CBC examination 22/10/2013 - Hb - 5.9g/dl, TLC – 2700/ cmm, Platelets – 66X 10eq/L. In view of pancytopenia marrow was done. Marrow biopsy was reported as EBV associated lymphoid proliferation – suspect Hodgkin's lymphoma. Aspirate was a dry tap and Flow cytometry was not done. serum LDH - 463 and B2microglbulin – 3.89.
PET scan - FDG avid but small cervical nodes maximum 1.9cm, max SUV 9.0. Mediastinal, axillary and abdominal nodes maximum 1.2cm max SUV 8.9 to 15.1.
Spleen is enlarged (20.5cm) and shows heterogeneous increased FDG uptake without any obvious lesions. Patchy heterogeneous increased FDG uptake in the marrow of all the visualized bone max SUV 12.9.
None of the nodes could be biopsied as they were tiny so final decision of treating as Stage IV B Hodgkin lymphoma with 6# of AEVD due to DLCO reduced. PET Scan post two cycles Complete response to Therapy CBC returned to normal in two cycles but platelet was 96 x 10e9/L (normal 150-400 x 10e9/L) Completed 6 cycles AEVD on March 2014 and Post therapy marrow was done which showed T cell excess with HRS cells but labeled as suspicious . In view of PET CMR patient was observed. Platelet raised to 115 (normal 150-400 x 10e9/L) and continue to range from 140 to 160 x 10e9/L. Last follow up was on 23/08/2017 and patient had no evidence of disease
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Marrow showed diffuse infiltration by fibrosis and inflmmatory ifniltrate with scattered Hodgkin-Reed-Sternberg like cells.
Immunophenotype: On immunohistochemistry these were CD30, EBVLMP1 and CD15 positive. CD20 and CD3 stained background cells. PAX5 was weak positive. MIB1 was cheifly seen in the large cells.
Cytogenetics: Not done
Molecular studies: not done
Proposed diagnosis: Classical Hodgkins lymphoma with primary marrow presenetation
Interesting feature(s) of submitted case: Primary presentation as pancytopenia and not dominant lymphadenopathy
Only after marrow diagnosis nodes were picked up but none was > 2cm.
CMR on PET scan but residual marrow cells
No evidence of disease in nearly 4 years follow up

EAHP18-BMWS-389

Intra-vascular bone marrow infiltration by indolent gamma/delta T-cell lymphoma

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Case description: 74 year-old male with 7-year history of mild neutropenia and thrombocytopenia, moderate splenomegaly, mild hepatomegaly and no lymphocytosis. Given the lack of complications, a watch-and-wait strategy was chosen. One year before bone marrow (BM) evaluation, fatigue and progressive weight loss ensued. After BM evaluation, cyclofosfamide was administered with little benefit; a subsequent CHOP regimen led to clinical improvement. At present (4 months after BM examination) the patient is in alive in good conditions.
Biopsy fixation details: The biopsy was fixed in formalin.
Frozen tissue available: n.a
Details of microscopic findings: Histological evaluation showed a mildly hypercellular BM (cellularity: 60%) with normal myeloid-to-erythroid ratio and preserved trilinear hematopoiesis. An intra-sinusoidal lymphoid infiltrate was noted, which consisted of medium-sized atypical cells with irregular nuclear contours and abundant cytoplasm. The atypical lymphocytes expanded the BM sinuses with little (if any) infiltration of the stroma. The atypical population accounted for about 15% of BM cellularity. Mild fibrosis (MF-grade 1) was present.
Immunophenotype: Lympohoid cells were positive for CD3, CD2, CD7, CD56, TIA1 and Perforin and negative for CD5, CD4, CD8, CD57, CD30, Granzyme B and EBER. The proliferation index was very low (5-10%).
Flow cytometry confirmed the immunohistochemical results, also detecting TCR gamma/delta, CD94 and KIR expression.
Cytogenetics: Normal karyotype (46, XY). FISH for 7q derangements was negative.
Molecular studies: Monoclonal TCR rearrangement was detected in the peripheral blood.
Proposed diagnosis: Bone marrow infiltration of gamma/delta T-cell lymphoma with hepatosplenic T-cell lymphoma (HSTL)-like features. The overall clinic-pathological findings suggest the differential diagnosis between an unusual, indolent form of HSTL and a gamma/delta T-cell lymphoma, NOS.
Interesting feature(s) of submitted case: This unusual case poses intriguing questions concerning the diagnosis of such gamma/delta lymphoid neoplasm. The clinical picture is in keeping with an indolent lymphoproliferative disorder (possibly, gamma/delta T-LGL), but several histological findings suggest an aggressive lymphoid neoplasm with features of HSTL. The differential diagnosis between gamma/delta T-LGL and HSTL is a true challenge. In recent years a series of clinic-pathological parameters have been proposed supporting the diagnosis of HSTL over gamma/delta T-LGL. These include: (i) severe clinical presentation; (ii) specific morphological features (i.e. expansion of BM sinuses by lymphoma cells; absence of azurophilic granules in neoplastic cells); (iii) typical immunophenotype (i.e. positivity for CD2, CD3, CD7, TIA1; negativity for CD5, CD4, CD8, CD57, Granzyme B and Perforin; variable expression of CD56); (iv) recurrent cytogenetic aberrations (isochromosome 7q; trisomy 8); and (v) detection of monoclonal TCR rearrangements.
Irrespective of the relatively indolent clinical course, the present case had several (but not all) HSTL-associated histological and cytogenetic features. In fact, the lymphoid cells disclosed clear-cut positivity for Perforin and lacked HSTL-associated cytogenetic derangements. The epidemiologic features of this tumor are also unusual for HSTL, as this lymphoma typically affects adolescents and young adults, being much rarer in elderly patients. Taken together, the overall findings of such case exclude a clear-cut gamma/delta T-LGL, favoring the diagnosis of an indolent gamma/delta T-cell lymphoma that possibly represents an atypical/unusual form of indolent HSTL.

EAHP18-BMWS-555

Bone marrow involvement by an angioimmunoblastic T-cell lymphoma obscured by a polytypic plasma cell proliferation

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Case description: A 64 yo man originating from Madagascar was admitted for rapidly progressive B symptoms (fever, asthenia) associated with auto-immune hemolytic anemia (positive Coombs test). Erythroblastopenia on the marrow smears. Treatment with steroids. A bone marrow biopsy was performed (slides submitted). A few weeks later, he developped generalized adenopathies without hepatosplenomegaly. An exicional inguinal lymph node biosy was performed . The patient received 2 cycles of Rituximab due to EBV reactivation. He died of disease a few days after diagnosis.
Biopsy fixation details: formalin-fixed
Frozen tissue available: No
Details of microscopic findings: The bone marrow biopsy is hypercellular showing an in infiltration by cells with a plasmacytic differentiation blending normal hematopietic cells; some of the cells ressemble mature plasma cells, others have larger nuclei and may sggest plasmablasts (CD138+, MUM1+, CD79a+, polytypic). In addition, there is a mild lymphoid infiltrate made of scattered atypical lymphocytes with abundant clear cytoplasm, often in small aggregates. These atypical lymphocytes are better emphasized by immunohistochemical staining with T (CD3+, CD5+, CD7+) and TFH (PD1+, ICOS+) markers and correspond to the IDH2R172K-positive cells.
The lymph node biopsy showed a relative effacement of the architecture by a neoplastic proliferation with a vague nodular pattern of growth. There are features of angioimmunoblastic T-cell lymphoma pattern I, as highlited by T-cell (CD2+, CD3+, CD5+, CD7+, TCRb(BF1)+, CD4+, CD8-) and TFH markers (CD10+, PD1+, ICOS+, CXCL13+). These neoplastic were also IDH2R172K-positive by IHC. In the internodular areas, there is a marked proliferration of B cells comprising a large component with plasmacytic polytypic proliferation (CD138+, MUM1/IRF4+, CD79a+) and a component of EBV-positive B blasts with an EBV latency type III (EBER+, LMP1+, EBNA2+).
Immunophenotype: see above
Cytogenetics: No
Molecular studies: PCR (g + IgH) (LN): clonal TCR and clonal IG gene rearrangement (FRI, FRII and Vk).
Allele-specific PCR : IDH2 R172K and RHOAG17V mutation.
Targeted NGS panel (1000x) :
- TET2 mutations : p.P941fs 34.5%, p.G641fs 13.8%, p.Q891X 7.1%, p.S315fs 2.8%
- RHOA (G17V) mutation (8,9%)
- IDH2R172K mutation (9,3%)
Serum dosage: elevated levels 2 hydroxy-glutarate (2HGA), the IDH2 onco-metabolite
Proposed diagnosis: Bone marrow involvement by an angioimmunoblastic T-cell lymphoma obscured by a polytypic plasma cell proliferation
Interesting feature(s) of submitted case: Clinical presentation with haemolytic anemia resulting in bone marrow trephine for diagnosis.
Bone marrow infiltration by AITL is obscured by a plasma cell proliferation and may have resulted in a misleading diagnosis of myeloma (in a context of hypergammaglobulinemia).
AITL involvement, also subtle, is highlighted by the lymphoid cell atypia (clear cell appearance), their TFH phenotype and positivity for IDH2R172K.
AITL diagnosis is further confirmed by the lymph node biopsy showing features of AITL (partly “early phase-pattern 1”) despite the full-blown clinical features, associated with an EBV-negative plasma cell proliferation and an EBV-positive clonal large B-cell proliferation
This EBV-positive lymphoproliferation shows an unusual latency type III suggestive of an immuno-compromised background.
The AITL has the prototypic genetic landscape with mutations in TET2, IDH2 and RHOAG17V
Immunohistochemistry for IDH2R172K identifies the mutation in neoplastic TFH cells both in the bone marrow and in the lymph node samples.
IDH2R172K mutation, like reported in AML, translates into serum high level of the onco-metabolite 2-HGA.

EAHP18-BMWS-127

Hepatosplenic T-cell lymphoma with unusual cytologic features

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Case description: This 47-year-old male presents with persistent fever, anorexia, weight loss and pancytopenia. He has a long history of rheumatoid arthritis, being treated with methotrexate, prednisone, and etanercept. In 2015, he was diagnosed with Felty's syndrome. Upon the current admission in 2017, extensive infectious, rheumatologic and pulmonary workups were negative. A CT scan showed splenomegaly, indeterminate pulmonary nodules and no adenopathy. PET scan was consistent with hepatosplenic and BM involvement by lymphoma and no hypermetabolic lymphadenopathy. Chemotherapy with CHOEP was begun. Thus far, after a few months, he has been tolerating the treatment well.
Biopsy fixation details: B5/decalcification.
Frozen tissue available: No.
Details of microscopic findings: Peripheral blood: Pancytopenia. HGB 9.1 g/dL; RBC 3.01 $x10^{12}$/L; MCV 91.0 fL; RDW 19.4 %; WBC 0.5 $x10^{9}$/L; PLT 34 $x10^{9}$/L.
BM aspirate: Sparsely cellular; aggregates of histiocytes. Differential cell count (500 cells): neutrophils 2%, myelocytes 3%, eosinophils 7%, basophils 1%, blasts 5%, normoblasts 44%, monocytes 3%, lymphocytes 33%, plasma cells 2%. Erythroid precursors with normoblastic maturation. Decreased myeloid precursors with normal maturation. Rare megakaryocytes seen. A subset of lymphocytes is atypical characterized by small to medium nuclei, irregular nuclear contours, and scant cytoplasm. Histiocytic hyperplasia is present with occasional hemophagocytosis.
BM biopsy: Hypercellular 90%. Erythroid precursors with normal morphology. Markedly decreased myeloid precursors. Abnormal interstitial and sinusoidal lymphocytic infiltrate, approximately 10-20% of cellularity, with a morphologic spectrum from predominately intermediate to large cells with multilobulated and/or irregular nuclear contours.
Immunophenotype: Immunohistochemical studies reveal an abnormal CD3 positive T-cell infiltrate which is also positive for CD2, CD5 (subset weak), CD7 (weak), TCR-gamma delta, and TIA1, and negative for CD4, CD8, TCR beta F1, and granzyme B. Epstein-Barr virus encoded RNAs (EBER) negative.
Cytogenetics: FISH on a clot section targeting specific areas with increased density of tumor cells showed 57% of nuclei with monosomy 7 and monosomy 8.
Molecular studies: No.
Proposed diagnosis: Hepatosplenic T-cell lymphoma.
Interesting feature(s) of submitted case: This is a challenging case of hepatosplenic T-cell lymphoma (HSTCL) due to the presence of unusual cytologic features (larger cells with pleomorphism) and lack of the typical genetic abnormality (ies) (isochromosome 7q, trisomy 8) in the setting of otherwise typical clinical (young, male patient; B-symptoms; hepatosplenomegaly) and pathologic features (bone marrow sinusoidal growth pattern, immunophenotypic characteristics of the tumor cells). Interestingly, this case is also an example of the rare presentation that has been reported in individuals with rheumatoid arthritis treated with tumour necrosis factor inhibitors.
In the majority of HSTCL cases, the cytologic appearance of the lymphoma cells shows little variation among patients. Neoplastic cells are usually monomorphic, small to medium lymphocytes containing small inconspicuous nucleoli. However, cytologic variations have occasionally been observed at diagnosis and may occur with disease progression. In our case, we observed, at diagnosis, a morphologic spectrum from predominantly intermediate to large cells with pleomorphic, irregular nuclei. This unusual cytology gives pause to the diagnostician and illustrates a challenge to hematopathologists to confidently diagnose and define such a rare entity as HSTCL, particularly in the absence of isochromosome 7q.

EAHP18-BMWS-158

CD30-positive ALK-negative T-cell lymphoproliferative disorder presenting in bone marrow and blood

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Case description: The patient was a 90 year-old woman who presented with fevers and pancytopenia (WBC 2.8x10^9/L, HGB 8.7 g/dL, PLT 38x10^9/L). She had a reported recent history (a few months prior) of pruritic skin lesions and a biopsy 2 months prior was reported as suspicious for T-cell lymphoma, but was not reviewed at our institution. She was treated with steroids and the lesions had resolved at the time of this admission. Atypical cells were seen in the peripheral blood and a bone marrow biopsy was performed. After the diagnosis was rendered, the patient opted for hospice care and expired one week later.
Biopsy fixation details: The trephine biopsy was fixed in zinc formalin and decalcified with hydrochloric acid/EDTA. The clot section was fixed in zinc formalin.
Frozen tissue available: None
Details of microscopic findings: The peripheral blood showed rare large and occasionally multinucleated cells, with moderately abundant, and occasionally granular, cytoplasm. The aspirate smear was aspicular and hemodiluted, but showed similar cells, rarely exhibiting erythrophagocytosis. On the trephine biopsy and clot section there were large cells with prominent nucleoli scattered throughout, without any specific pattern of infiltration. Some cells had reniform of horseshoe-shaped nuclei, while others were bi- or multinucleated.
Immunophenotype: Immunohistochemistry
Positive: CD3, CD4, CD7 (subset, dim), CD30 (strong, diffuse membrane and Golgi staining), TIA-1, granzyme B, perforin
Negative: CD8, CD15, CD20, CD61, CD71, PAX5, ALK, P63
Cytogenetics: 52,XX,+1,-4,+5,+6,del(6)(q21),del(6)(q21),+20,+22[cp2]/46,XX[19]
Molecular studies: None
Proposed diagnosis: Anaplastic large cell lymphoma, ALK-negative, presenting in the bone marrow and peripheral blood.
Interesting feature(s) of submitted case: This is a case of a CD30-positive T-cell lymphoproliferative disorder with prominent bone marrow and also peripheral blood involvement, but no evidence of nodal disease. There may have been antecedent presentation in the skin, however those lesions were relatively recent and had resolved with minimal therapy by the time of this bone marrow. This could represent an anaplastic large cell lymphoma (ALCL), ALK-negative with predominantly bone marrow (and potentially skin) involvement, primary cutaneous (PC-)ALCL with dissemination to bone marrow but not regional lymph nodes, or a peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Given the strong CD30 staining, positivity for cytotoxic markers, and hallmark cells, an ALCL is favored. Lossed os 6q21 have been described in both PC-ALCL and ALCL, ALK-negative. Gains of 1q, 6p are described as occurring more often in ALCL-ALK negative than in PTCL-NOS. However the poor prognosis would be more consistent with either a TP63 translocated ALCL (PC or ALK-negative, effectively excluded by lack of p63 staining by IHC) or PTCL-NOS.

EAHP18-BMWS-173

57 year old man with sinusitis and pancytopenia

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Case description: A 57 year old man with chronic sinusitis (treated with antibiotics and steroids) presented to an outside hospital (OSH) with 6 mo of fatigue/weight loss, recent fevers (103F) and pancytopenia. Imaging showed mild hepatosplenomegaly. He was given broad-spectrum antibiotics. OSH bone marrow biopsy was hypercellular with some hemophagocytosis, no blast increase and no phenotypic or karyotypic abnormalities. He transferred to NYPH where initial laboratory studies showed pancytopenia (WBC 0.6K/uL, HGB 10.1g/dL [transfused], platelets 13K/uL); DIC; liver failure; renal failure; elevated triglycerides; and elevated ferritin. Infectious disease workup only showed an Epstein Barr virus (EBV) viral load of >400,000 cpy/mL. A presumptive clinical diagnosis of hemophagocytic lymphohistiocytosis (HLH) was rendered. A bone marrow biopsy was done. PET scan showed FDG avid cervical lymph nodes and nasal cavity mucosa prompting lymph node/nasal cavity biopsies. He was treated with etoposide, steroids, gemcitabine and oxaliplatin. He developed E. coli sepsis, had progressive renal and liver failure and died.
Biopsy fixation details: Bouins fixation; EDTA-based decalcification
Frozen tissue available: No
Details of microscopic findings: The bone marrow was hypercellular, but disorganized. The myeloid to erythroid ratio was increased with a left-shift in the granulocytes. Increased numbers of mononuclear cells were seen including lymphocytes and monocytes/macrophages. These cells were scattered throughout the marrow without prominent collections. Megakaryocytes were dysplastic and often small with scant cytoplasm and hyperchromatic nuclei. Hemophagocytosis and atypical mononuclear cells were seen in the aspirate.
Immunophenotype: Flow cytometry: CD19+B cells: Polytypic. CD3+T cells: CD2+,CD5+,CD7+, CD4/CD8=1.4. Lymphocytes: CD3+, CD5+=22%; CD7+, CD2+=90%; CD4=13%; CD8=10%; CD56=71%; TCRA/B=24%; TCRG/D=<1%. CD34+ cells:<1%.
Bone marrow core biopsy immunohistochemistry/ISH: Increased scattered CD3, CD56, TIA1, granzyme B and perforin positive cells; CD68 (KP1) many; CD20 rare; EBER frequent scattered
Cytogenetics: FISH: Negative for monosomy 5, monosomy 7, deletions of 5q31, 7q31, and 20q12 regions and trisomy 8
Molecular studies: No TCR rearrangement; myeloid molecular panel negative
Proposed diagnosis: Extranodal NK/T cell lymphoma, nasal type, with hemophagocytic lymphohistiocytosis (HLH)
Interesting feature(s) of submitted case: The pattern of infiltration (scattered and sometimes linear/vascular) of the EBV infected cells and the pattern and number of CD56+ cells in the marrow is unusual. In light of the history (presumed diagnosis of HLH, high EBV titers, immunosuppression) and the biopsy findings, there were several diagnostic possibilities, including (1) fulminant HLH secondary to EBV infection with a large number of reactive NK/T cells; (2) iatrogenic EBV+ B cell lymphoproliferative lesion lacking expression of the usual pan-B cell markers, with an associated reactive NK/T cell response and EBV-driven HLH; (3) iatrogenic EBV+ hepatosplenic T cell lymphoma with associated HLH; (4) aggressive NK cell leukemia associated with HLH; and (5) unusual presentation of extranodal NK/T cell lymphoma, nasal type, with associated HLH. The bone marrow is an unusual site for the primary diagnosis of extranodal NK/T cell lymphoma, nasal type. However, in light of the patient's history of chronic sinusitis, this may be due to a longer than usual history of untreated disease. The subsequent nasal biopsy showed extranodal NK/T cell lymphoma, nasal type, with angiodestruction and necrosis, which confirmed the diagnostic suspicion.

EAHP18-BMWS-188

Hepatosplenic T cell lymphoma in a 30 year-old female primarily diagnosed in bone marrow

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Case description: This was a 30-year-old female, who presented with a chief complaint of pre-syncope for 1 month and intractable epistaxis upon admission. Physical examination (PE) noted diffuse ecchymosis and splenomegaly. A computerized tomography scan of the abdomen and pelvis found marked hepatosplenomegaly. No lymphadenopathy or other organomegaly was found on PE or imaging studies. A complete blood count performed at initial evaluation demonstrated a moderate normocytic anemia and severe thrombocytopenia. Although her white cell count was within normal range, ~5% atypical lymphoid cells were found on the peripheral blood smear.

Biopsy fixation details: The patient underwent a trephine core biopsy from the left posterior iliac crest with one bone marrow biopsy core but no aspirated marrow particles obtained. Buffy coat smears and touch imprints of the bone marrow core biopsy were air-dried and stained with Wright-Giemsa. The bone marrow biopsy was fixed in 10% neutral-buffered formalin, decalcified for 3 hours and then embedded in paraffin, sectioned at 3- to 4-µm and stained with hematoxylin-eosin and/or counterstained with hematoxylin for immunohistochemistry.

Frozen tissue available: Not performed.

Details of microscopic findings: The buffy coat smears and touch imprints show frequent medium to large-sized atypical lymphoid cells (~73% based on 400-cell differential count on touch imprints) with large convoluted nuclei, hyperchromatic chromatin, multiple nucleoli, and small amount of agranular deeply basophilic cytoplasm. Histologically, the bone marrow is hypercellular for age (>90% cellularity) with homogeneous sheets of atypical lymphoid cells which infiltrate the marrow in a sinusoidal/interstitial pattern mottled with occasional histiocytes and rare residual granulocytes and megakaryocytes. The cells are morphologically similar to that of the marrow core biopsy touch imprints.

Immunophenotype: Immunohistochemically, the atypical cells are positive for CD3, but negative for PAX5, TdT, granzyme B, perforin, TIA-1, and CD30. Flow cytometry shows an abnormal cell population (~45% of total events) expressing CD2, CD3, CD7, CD8, CD38, CD45, CD56, and TCR γ/δ, but not expressing CD1a, CD4, CD5, CD10, CD20, CD30, CD34, HLA-DR, TdT, TCR α/β, or other myeloid antigens.

Cytogenetics: Chromosomal analysis on bone marrow aspiration showed 46, XX. T cell lymphoma FISH studies on bone marrow aspiration were normal.

Molecular studies: T-cell receptor gene rearrangement analysis on bone marrow aspiration was positive.

Proposed diagnosis: Peripheral (mature) T-cell lymphoma, most compatible with hepatosplenic T-cell lymphoma (HSTL)

Interesting feature(s) of submitted case: This case represents a HSTL primarily diagnosed in bone marrow. Massive splenomegaly, lymphocytes devoid of azurophilic granules, and γδ T-cell receptor type are the most important features that support the diagnosis of HSTL in this case. HSTL in bone marrow involvement usually presents with sinusoidal involvement, but in more advanced stages such as in this case, near complete replacement of the marrow may mask the typical pattern. The classic cytogenetic anomaly for HSTL (isochromosome 7) is not detected. The granule-associated proteins are all negative in immunohistochemical stains in this case. These may represent a variant phenotype of HSTL.

EAHP18-BMWS-194

Angio-immunoblastic T-cell lymphoma presenting with bone marrow failure

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Case description: This 73 year old Caucasian male had acute myeloid leukaemia (FAB M4 – Core binding factor positive) (AML with CBFB-MYH11) in 2002, treated with Daunorubicin and Cytarabine. He was in complete remission since 2003 but developed immune thrombocytopaenic purpura (ITP) in March 2017. ITP was treated with steroids and immunoglobulin. 5-6 months later, he developed pancytopaenia (Hb 74 g/L, WBC 3.8 x 10^9 /L, Neutrophil 2.1 x 10^9 /L, Lymphocyte 1.4 x 10^9 /L, Platelet 53 x 10^9 /L) and skin rash. CT scan showed prominent mesenteric and para-aortic lymph nodes, and slightly prominent (but with fatty hila, possibly reactive) axillary and inguinal lymph nodes. Moderate ascites and splenomegaly (23 cm) were noted but there was no pleural effusion or hepatomegaly. Immunoglobulin levels were normal. HIV serology and autoantibodies were all negative but C3 level was slightly low at 0.69 g/L (range 0.75 – 1.65). There was no evidence of haemolysis. Bone marrow trephine biopsy and skin punch biopsy were performed. Skin rash resolved completely on steroid therapy. Lymphadenopathy also largely subsided but recurred later and a needle core biopsy of axillary lymph node was performed. His general condition deteriorated and he died shortly afterwards before any chemotherapy.
Biopsy fixation details: Formal acetic alcohol with 10% formic acid decalcification
Frozen tissue available: No
Details of microscopic findings: Aspirate: Aparticulate and non-contributory.
Trephine: Hypercellular marrow with a focal nodular and paratrabecular lympho-histiocytic infiltrate of small, medium sized and large lymphoid cells. Admixed scanty plasma cells and eosinophils present.
Skin: A moderate perivascular dermal lymphoid infiltrate comprising of small, medium sized and large lymphoid cells.
Lymph node: A diffuse infiltrate of medium sized lymphoid cells, including some clear cells, admixed with histiocytes.
Immunophenotype: Immunohistochemistry (bone marrow / skin / lymph node):
Majority of lymphoid cells (small, medium and large):
+ve: CD2, CD3, CD5, CD4, PD1, CXCL13, ICOS, BCL6 (variable), CD30 (in some), CD7 (slight reduced expression), High Ki67 proliferation.
-ve: CD10, CD8, CD20, CD79a, Pax 5, EBER-ISH, CD15, CD56, TIA1, Granzyme B, Myeloperoxidase, CD34, ALK1.
Scattered large and some admixed lymphoid cells:
CD20+, CD79a+, Pax 5+, EBER-ISH-
CD21: Marked abnormal follicular dendritic cell (FDC) proliferation in lymph node. A focus of possible FDC proliferation in bone marrow.
Cytogenetics: Not available.
Molecular studies: Clonal TCR gene rearrangement in TCR Beta VBJ-C and TCR Gamma VGJ-A by PCR on skin. PCR on bone marrow trephine failed.
Proposed diagnosis: Tumour-cell rich 'Angio-immunoblastic T-cell lymphoma' occurring post-therapy in AML and presenting with bone marrow failure
Interesting feature(s) of submitted case: Unusual presentation, predominantly with bone marrow failure in a patient with treated AML, hence first clinically suspecting relapsed AML or therapy related MDS. Unusual bone marrow histology (tumour-cell rich pattern) with diagnostic difficulty (on bone marrow trephine biopsy alone).

EAHP18-BMWS-239

Primary bone marrow peripheral T cell lymphoma with T-follicular helper phenotype

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Case description: 67 year old male presented with weight loss and pruritic rash. PET scan shows bone marrow lesions. No lymphadenopathy, masses, visceral lesions or organomegaly.
Biopsy fixation details: Bouins, EDTA and 10% buffered formalin.
Frozen tissue available: No
Details of microscopic findings: Sections show bone marrow. The marrow is hypercellular for age. All haemapoietic cell lineages are present but they are reduced and replaced by a diffuse lymphoid infiltrate. The lymphoid cells are medium in size and contain scant cytoplasm. The nuclei are irregular and display inconspicuous nucleoli. The atypical lymphoid infiltrate also contain numerous mitoses.
Immunophenotype: Positive: CD45RO, CD2, CD4, bcl-6, PD-1, CXCL13, TIA-1, CD30, granzyme B.
Negative: CD3, CD5, CD7, ALK, CD20, CD21, CD35, TCR BF-1, TCR delta, EBER ISH, CD10, CD56
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Primary bone marrow peripheral T cell lymphoma with T-follicular helper phenotype
Interesting feature(s) of submitted case: Primary bone marrow presentation of peripheral T cell lymphoma with T-follicular helper phenotype. No lymphadenopathy or visceral disease present.

EAHP18-BMWS-257

Challenging case of gamma delta T-cell lymphoma with precursor T- cells and marked eosinophilia

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Case description: 3 years old female child, presented with fever for 10 days. Complete blood count showed a Hb of 10.1 g/dl, platelets count of 127x103/uL, and marked leucocytosis with WBC count of 110 x103/uL. CT showed anterior mediastinal mass, multiple bilateral cervical, left supraclavicular, right paratracheal with bilateral axillary, bilateral inguinal and external iliac lymph nodes enlargement with sever hepatosplenomegaly. Patient underwent bone marrow aspirate and biopsy with biopsy from the mediastinal mass and a diagnosis of gamma/delta T cell neoplasm with increased blasts and eosinophilia was concluded. The patient started initially on Imatinib & continued for 20 days with significant reduction in WBC count down to 30,000. Subsequently BFM 2009 Protocol for T-cell lymphoblastic leukaemia/lymphoma was given. Day 15 evaluation CT showed significant reduction of lymph nodes, mediastinal mass and spleen size and bone marrow showed persistent increase in gamma delta T -cells population. Decision was taken to shift to lymphoma protocol.
Biopsy fixation details: Paraffin embedded biopsy fixed in AZF & formalin fixed paraffin embedded biopsy.
Frozen tissue available: NA
Details of microscopic findings: Peripheral smear showed leucocytosis with lymphocytosis, marked eosinophilia with left shift, neutrophilia with left shift, dysplastic features and monocytosis. Differential count showed 8% neutrophils, 63% Lymphocytes, 22% Eosinophils, 1% Basophils, 2% Monocytes, 1% Metamyelocytes, 1% Myelocytes and 2% Blasts. The lymphoid cells were small to medium sized mature looking (condensed chromatin) and many atypical with nuclear irregularities, some cells seen with open chromatin and one or more nucleoli. Bone marrow aspirate and biopsy were hypercellular (100% cellularity) with increased eosinophils and extensive diffuse infiltration by gamma/delta T-cells with increased blasts (12%). IHC stains showed diffuse infiltration by CD3 positive cells with increased positivity for TdT and CD99. Biopsy of mediastinal mass showed involvement by T-cell lymphoma.
Immunophenotype: Flow cytometry on bone marrow aspirate showed an abnormal population of T-cells comprising ~ 30% expressing CD45 (moderate to bright), sCD3, cCD3, CD5, CD7, TIA1, and TCR gamma/delta with partial expression of CD8 and CD2 while negative for Tdt & CD34. There was as well ~7% precursor T- cells expressing cCD3, sCD3, CD5, CD7, TdT, double positive for CD8, CD4 & TCR gamma/delta with partial CD1a.
Cytogenetics: FISH analysis for BCR -ABL 1 and 4q12 (FIP1L1-PDGFRA), TRA/D, FGFR1 (8P11.2), ABL2, CHIC2, PDGFRB, and ABL1 are normal.
Karyotype:46,X,?del(X)(p21),der(5)t(5;15)(q22;q15),?inv(8)(p23q13),der(10)add(10)(p13)del(10)(q24),del(11)(q21q22),add(13)(q34),del(15)(q21)[13]/46,XX[47].
Molecular studies: Molecular analysis for T- cell receptor gene rearrangement is positive (a partial T-beta (D-J) rearrangement and T-gamma rearrangements). No evidence of the JAK2 V617F mutation.
Proposed diagnosis: Gamma/ Delta T-Cell neoplasm with T- lymphoblastic leukaemia component and marked eosinophilia.
Interesting feature(s) of submitted case: The combination of gamma delta T- cell lymphoma cells with T-cell precursors, is it T- cell lymphoma evolving to acute leukemia or 2 different pathology ?. Although the marker for clonal eosinophilia were negative, the presence of marked eosinophilia with dysplasia in eosinophils & granulocytic cells with the good response to imatinib render the exclusion of a myeloid neoplasm component is difficult as well.

EAHP18-BMWS-303

A clonal T-cell expansion, possibly reflecting an unusual (and early) primary bone marrow presentation of a gamma delta T-cell lymphoma

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Case description: An 84-year-old male with no contributory prior medical history presented with thrombocytopenia. A bone marrow biopsy was obtained.
Biopsy fixation details: Buffered zinc formalin and decalcification.
Frozen tissue available: No.
Details of microscopic findings: H&E stained sections of the bone marrow biopsy show a mildly hypercellular marrow for age (~30%) with normal trilineage hematopoiesis. No overt histologic evidence of a lymphoid infiltrate is evident. The aspirate smear and touch preparation are suboptimal.
Immunophenotype: Flow cytometry reveals the presence of ~55% CD2+ sCD3+ T-cells that show slight down regulation of CD5 and CD7 expression, and include a major subset (22%) that is double negative (CD4- CD8-). There are admixed NK cells (5%) and T-LGLs (7%), as well as rare (1%) polytypic B-cells.
Immunohistochemical studies show the presence of scattered CD3+ T-cells (~10-20%) that are mostly distributed singly, with only a few small clusters evident; no sinusoidal distribution is noted. CD20+ B-cells are infrequent (<5%). The T-cells express TCRgamma, granzyme B, perforin and TIA1. They are negative for TCRbeta, CD1a, TCL1, TdT, and ALK.
Cytogenetics: N/A.
Molecular studies: A monoclonal TRG gene rearrangement is detected by PCR.
Proposed diagnosis: A clonal T-cell expansion, possibly reflecting an unusual (and early) primary bone marrow presentation of a gamma delta T-cell lymphoma.
Interesting feature(s) of submitted case: This case demonstrates a histologically inapparent clonal gamma-delta T-cell expansion that might reflect an early and apparently exclusive presentation in the bone marrow. An abnormal population was initially detected by flow cytometry, with subsequently detected corroborating immunohistochemical features.
Lymphomas of gamma-delta T cells tend to be aggressive and typically occur at one of three extranodal sites: in the skin as primary cutaneous gamma-delta T-cell lymphoma, in the liver and spleen as hepatosplenic T-cell lymphoma, and in the gastrointestinal tract, typically as monomorphic epitheliotropic intestinal T-cell lymphoma or less commonly as enteropathy-associated T-cell lymphoma. Primary presentation of a gamma-delta T-cell lymphoma in the bone marrow without clinical features consistent with one of the classic anatomic locations being involved is an extremely rare occurrence. Accordingly, any patient presenting in this manner should undergo thorough evaluation of the implicated primary extranodal sites of involvement. However, none was apparently evident in this patient who was unfortunately lost to follow-up.

EAHP18-BMWS-322

What's in a name? Is a hepatosplenic T-cell lymphoma diagnosed in the bone marrow without liver involvement still a hepatosplenic T-cell lymphoma?

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Case description: A 65-year-old man with a history of Crohn disease on chronic azathioprine had been hospitalized multiple times over the past few months for recurrent fevers, night sweats, weight loss, confusion, epistaxis, pancytopenia, hepatosplenomegaly, polyneuropathy and hemophagocytic lymphohistiocytosis. A bone marrow biopsy revealed plasma cell myeloma (PCM) and a T-cell lymphoma suggestive of hepatosplenic T-cell lymphoma (HSTCL). Liver biopsy showed cirrhosis but not lymphoma (material not available for review).
Biopsy fixation details: Buffered zinc formalin and Rapid decal
Frozen tissue available: No
Details of microscopic findings: The borderline quality bone marrow aspirate smear shows increased numbers of mostly normal-appearing plasma cells (~15%). Lymphocytes (7%) are mostly morphologically normal, but rare (<1%) irregular medium-sized cells with vacuolated, deeply basophilic cytoplasm are seen.
The bone marrow biopsy shows a hypercellular marrow (80%) expanded by plasma cells (~20%) and scattered and clustered lymphoid cells (~20%).
Immunophenotype: Immunostains document two neoplasms:
1. CD2+ CD3+ CD7+ T-cells (~25%) that coexpress CD8, TCRγ and perforin but are negative for CD1a, CD4, CD5, CD30, CD56, CD57, TCRβ, granzyme B, ALK and EBER1. These cells are distributed singly, in clusters and in linear arrays suggesting possible intrasinusoidal growth. CD34 highlights a few endothelial cell-lined sinusoids with an accumulation of these cells, but CD31 and vWF do not show compelling evidence of T-cell confinement to sinusoids.
2. Focally clustered lambda-restricted CD138+ plasma cells (~25%).
Cytogenetics: 46,XY[20]
Myeloma FISH studies show monosomy 13 and trisomy 5.
FISH for iso(7q) could not be performed.
Molecular studies: Monoclonal TRG gene rearrangement by PCR
Proposed diagnosis: 1. Hepatosplenic T-cell lymphoma (?)
2. Plasma cell myeloma
Interesting feature(s) of submitted case: This is an unusual case with two distinct synchronous hematologic neoplasms in the bone marrow—a T-cell lymphoma and PCM. PCM may coexist with other lymphoid malignancies, most commonly chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis. While occasional association with various subtypes of peripheral T-cell lymphomas has been documented, development of the second lymphoma is usually metachronous. Only rare cases of simultaneous occurrence with a T-cell neoplasm (anaplastic large cell lymphoma, PTCL-NOS, and angioimmunoblastic T-cell lymphoma) have been reported in the literature.
The T-cell lymphoma is of gamma-delta lineage with many features that are compatible with HSTCL, including the history of hemophagocytic syndrome and Crohn disease treated with azathioprine, both of which are associated with this lymphoma.
However, the classic intrasinusoidal growth pattern could not be unequivocally documented and the liver biopsy was negative for a lymphoma, raising the question of whether the diagnosis of HSTCL can be made in the absence of both this growth pattern and hepatic involvement. It has been noted in the literature that the pattern of bone marrow involvement becomes increasingly interstitial with a shift toward larger blastic cells with disease progression.

EAHP18-BMWS-349

T/NK cell leukemia with lack of surface or cytoplasmic CD3, mature NK-cell phenotype, and clonal T-cell receptor gene rearrangement.

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Case description: 33y/o M, previously healthy, complained of eye rash x 3 days. Exam revealed periorbital erythematous rash and scleral icterus. Work-up revealed pancytopenia (WBC 1.0, Hgb 12.5, PLT 13), elevated LFTs, and hepatosplenomegaly. Bone marrow biopsy revealed 60% atypical lymphocytes with mature NK-cell phenotype and lack of surface or cytoplasmic CD3 by flow cytometry. EBV was negative. A diagnosis of aggressive NK-cell leukemia (EBV-negative) was made. Subsequent skin biopsy showed an epidermotropic lymphoid infiltrate with similar phenotype. Clonal T-cell receptor (TCR) gene rearrangement was identified in the skin. Identical clonal TCR peaks were subsequently identified in the bone marrow. The diagnosis was then modified to peripheral T-cell lymphoma, not otherwise specified.
Biopsy fixation details: Formalin fixation and decalcification
Frozen tissue available: No
Details of microscopic findings: In PB and paucicellular BM smears, atypical lymphocytes are intermediate in size and have condensed chromatin, irregular nuclear folds, occasional nucleoli, and moderate agranular cytoplasm. In the BM core, the marrow is 95% cellular with 60% atypical lymphocytes in a diffuse interstitial pattern. They are intermediate to large with hyperchromatic condensed chromatin, irregular nuclear folds, occasional nucleoli, and moderate clear cytoplasm. In the skin, an atypical epidermotropic lymphoid infiltrate has similar morphologic features to the BM core.
Immunophenotype: Positive: CD2 (weak), CD3 (by IHC), CD7 (bright), CD8, CD16, CD45, CD52, CD56, CD99 (weak), TIA-1. (Skin is similar, but with weak CD7 and negative CD56)
Negative: surface/cytoplasmic CD3 (by flow), CD4, CD5, CD20, CD34, CD57, EBNA2, granzymeB, LMP, PAX5, TCRα/β, TCRγ/δ, TdT
Cytogenetics: Chromosomes: 46,XY
FISH: trisomy 7 (25%), extra copy of 7q31 (5%), extra copy of 8q22 (21.5%), and extra copy of 21q22 (5%)
Molecular studies: EBER-ish: negative
NGS: DNMT3A p.R882H and KRAS p.G12A
TCR gene rearrangement: positive, with identical peaks in bone marrow and skin
Proposed diagnosis: Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
Interesting feature(s) of submitted case: The unusual combination of mature NK-cell phenotype, lack of surface or cytoplasmic CD3 by flow cytometry, and clonal TCR gene rearrangement made this case challenging to classify. Multiple diagnoses were initially considered, including hepatosplenic T-cell lymphoma (HSTCL), T-lymphoblastic lymphoma (T-ALL), aggressive NK-cell leukemia (aNKL), and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Lack of intrasinusoidal infiltration and lack of surface CD3 and TCR argued against HSTCL. Lack of CD34, TdT, and cytoplasmic CD3 with expression of the mature NK-cell antigen CD16 argued against T-ALL. The distinction between EBV-negative aNKL and PTCL-NOS was more difficult. The mature NK-cell phenotype and lack of surface TCR and cytoplasmic CD3 by flow cytometry would seem to argue against a T-cell neoplasm. We wondered whether this could represent an NK-cell derived from a thymocyte with failed nonfunctional TCR gene rearrangements. Small subsets of NK-cells with thymic origin and TCR gene rearrangement were previously described in mice[1], but these cells were later proven to be NK-like γ/δT-cells rather than true NK-cells[2,3]. Thus for classification purposes, the presence of TCR gene rearrangement in a mature lymphoid neoplasm is currently considered pathognomonic for a T-cell process, solidifying the diagnosis as PTCL-NOS in this case. This case also underscores the necessity of TCR gene rearrangement studies in all cases of suspected NK-cell leukemia, regardless of phenotype by flow cytometry.

EAHP18-BMWS-383

22 year-old man with EBV-positive indolent NK-cell lymphoproliferative disorder in peripheral blood and bone marrow

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Case description: The patient is 22 year-old Puerto Rican man. He was in good health until 2011 when he was diagnosed with mononucleosis. In 2012, he presented with fever, abdominal pain, and diarrhea. He then developed ARDS, requiring intubation for 2 weeks. Bone marrow biopsy was performed due to persistent fever, and findings were unremarkable. In January 20 17, he was again admitted to a hospital due to fever. Hepatosplenomegaly was noted. He did not have lymphadenopathy or skin lesions. Bone marrow biopsy showed atypical NK-cell population, and many EBV-positive cells were present. He was transferred to our institution with presumptive diagnosis of aggressive NK-cell leukemia. His CBC was unremarkable with mild monocytosis (WBC 9400/ul, Hgb 12.9 g/dL, Plt 319000/ul, neutro 27%, lymph 51%, mono 21%). Plasma EBV PCR copy number was markedly elevated (187,828 copies/ml, 5.27 log)
Biopsy fixation details: 10% formalin
Frozen tissue available: No
Details of microscopic findings: Bone marrow biopsy: Marrow is mildly hypocellular for age (approximately 50% cellularity). Trilineage hematopoiesis is observed without increase in blasts. EBER-ISH showed many positive cells on the core biopsy.
Peripheral blood smear: Many large granular lymphocytes were noted.
Immunophenotype: Flow cytometric analysis done on bone marrow aspirate detected atypical NK/T-cell population with CD2-/ sCD3-/ CD4-/ CD5-/ CD7 bright+/ CD8+/ CD56 bright+ immunophenotype (4.9% of total WBCs). Immunohistochemistry performed on bone marrow core biopsy also showed increased atypical NK/T-cell population, and EBER-ISH highlighted many cells on the core biopsy.
Atypical NK/T-cell population similar to that seen in bone marrow aspirate sample was detected also in peripheral blood (17.9% of total WBCs).
Cytogenetics: 46, XY[20]
Molecular studies: The comprehensive genomic sequencing was performed using Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets platform (MSK-IMPACT HEME) This is a hybridization capture-based next-generation sequencing assay for targeted deep sequencing of all exons and selected introns of 401 key cancer genes known to be altered in hematological malignancies. Barcoded libraries from patient tumor and matched normal samples are captured, sequenced, and subjected to a custom analysis pipeline to identify somatic mutations. By this assay, STAT3 exon21 Y640F mutation was identified.
Germline genetic testing with skin fibroblasts: Mutation associated with Hemophagocytic lymphohistiocytosis: Negative. Microarray for copy number variations: Negative
Proposed diagnosis: NK-cell lymphoproliferative disorder, EBV-associated
Interesting feature(s) of submitted case: With presumptive diagnosis of aggressive NK-cell leukemia, while waiting for definitive diagnosis, he was treated with dexamethasone and acyclovir. During this time, his fever subsided. His EBV titers declined, and dexamethasone was discontinued after 4 days. He did not receive chemotherapy. Plasma EBV PCR was not detected on 8/28/2017, however, he still presents with atypical NK/T-cell population in peripheral blood (1.1% of WBC, last follow up 9/25/2017). This case shows that not all cases of EBV positive NK-cell proliferations in the blood represent aggressive NK-cell leukemia. This case lacks complex genetic alterations, and shows STAT3 mutation, reported in 30% of patients with chronic lymphoproliferative disorder of NK cells (Jerez A. et al. Blood 2012). EBV-positive indolent NK-cell lymphoproliferative disorder is an important differential diagnosis of aggressive NK-cell leukemia, and may help for avoiding unnecessary toxic therapy.

EAHP18-BMWS-384

Hepatosplenic T cell lymphoma, alpha-beta type, with CD31 (PECAM-1) expression and mutations in the genes associated with common gamma chain-signaling and in ATM gene in a patient on immunosuppressive therapy for Crohn's disease

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Case description: A 27-year-old male presented with abdominal discomfort, nausea, vomiting, and shortness of breath. He has Crohn's disease and has been on azathioprine for a few years. LFTs are elevated and he has moderate leukocytosis (38.7 K/ul), marked thrombocytopenia (24K/ul), palpable hepatosplenomegaly, and no palpable lymphadenopathy. CT scan of abdomen and pelvis shows marked hepatosplenomegaly and no other abnormality. CT scan of chest shows no abnormality. Peripheral blood smear shows 45% large lymphoid cells. Bone marrow aspirate was a dry tap and bone marrow core had crush artifact. Aspirate clot sections, bone marrow core touch preparations and flow cytometric analysis of the peripheral blood as well as of hemodiluted bone marrow aspirate were used for interpretation and a diagnosis of hepatosplenic T-cell lymphoma of alpha-beta type was made. 6 cycles of Hyper-CVAD were planned. He developed neutropenic fever and CSF involvement after first cycle and is waiting to start the second cycle.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: No
Details of microscopic findings: Peripheral blood and markedly hemodiluted bone marrow aspirate smears showed about 45%>50% large lymphoid cells with slightly condensed chromatin, prominent nucleoli and vacuolated cytoplasm, and many NRBCs. H and E sections of the aspirate clot showed many large lymphoid cells with high N:C ratio, irregular nuclei and slightly condensed chromatin. H and E sections of the bone marrow core showed crush artifact, but a sinusoidal and extrasinusoidal pattern of large lymphoid cell infiltration could be appreciated. As core biopsy sections lost most of the non-crushed tissue in the immunostained sections, aspirate clot sections were used for immunostains.
Immunophenotype: Positive immunostains in lymphoid cells: CD2, CD3, CD7, CD31, TIA-1, p53, and Ki67 (~95%); **Negative immunostains in lymphoid cells:** CD1a, CD4, CD5, CD8, CD30, CD34, EBV-LMP1, EBER (by ISH), granzyme B, perforin, and TdT. **EBER by ISH** was negative. **Flow cytometric immunophenotype of lymphoma cells:** CD2+, CD3+, CD7+, CD4-, CD5-, CD8, CD99+(dim), TCRαβ+, CD16+(dim), CD56-, CD57-, TdT-, CD34-, CD1a-, CD30-
Cytogenetics: Abnormal male karyotype with isochromosome 7,trisomy 8 and loss of Y chromosome
Molecular studies: TCR beta and gamma gene rearrangements are detected. **FISH of bone marrow aspirate:** Gain of 7q with concurrent loss of 7p, suggestive of Isochromosome 7. **Next-Generation Sequencing using 128-gene panel:** Pathogenic mutations are detected in ATM gene, JAK1 gene, JAK3 gene, and KMT2D gene. Mutations of uncertain significance are detected in ATM, DIS3, GNA13, and NF1 genes.
Proposed diagnosis: Hepatosplenic T cell lymphoma, alpha-beta type, with CD31 (PECAM-1) expression and mutations in the genes associated with common gamma chain-signaling and in ATM gene
Interesting feature(s) of submitted case: (1) Hepatosplenic T cell lymphoma (HSTCL) of alpha-beta type shows three most common cytogentic abnormalities seen in HSTCL (isochromosome 7, trisomy 8 and loss of chromosome). (2) HSTCL shows CD31 expression, which is considered to be cytoprotective due to inhibition of apoptosis and a suppressor of anti-tumor T cell responses, and therefore, may promote lymphoma development and may also confer chemoresistance. (3) Concurrent mutations in the genes associated with common gamma-chain JAK-STAT signaling pathway (JAK1 and JAK3 in our case) and in ATM has been suspected to be pathogenetically important in HSTCL.

EAHP18-BMWS-402

ALK+ Anaplastic Large Cell Lymphoma with peripheral blood and bone marrow presentation.

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Case description: 40 year old female was admitted with abdominal pain and sepsis. Peripheral blood counts revealed a leucocytosis, composed predominantly of neutrophils and a moderate thrombocytopenia. Peripheral blood counts were as follows: haemoglobin concentration:102g/L, white cell count 62.4 x 10^9/L, platelet count 98 x 10^9/L. A peripheral blood smear was examined and was noted to be leucoerythroblastic, containing large abnormal mononuclear cells with complex nuclei and prominent nucleoli. CT scan revealed splenomegaly with splenic infarcts and enlarged axillary and mesenteric nodes. The patient became very unwell requiring ITU admission and an urgent diagnosis was required.
Biopsy fixation details: 10% Formalin fixed, decalcified in EDTA.
Frozen tissue available: No
Details of microscopic findings: Blood film: Leukoerythroblastic blood film. Large atypical cells account for approximately 15% of cells. These are pleomorphic with complex nuclei and basophilic,sometimes vacuolated cytoplasm. High N:C ratio with intermediate chromatin texture. Several have one or more nucleoli.
Bone marrow aspirate: Hypercellular particulate bone marrow aspirate with approximately 3% atypical lymphoid cells similar in morphology to those described in the peripheral blood.
Bone marrow clot preparation: There is a population of large, highly atypical cells with complex nuclear structure.
Immunophenotype: Peripheral blood: Flow cytometry was performed and the cells were found to express CD2 (37%), weak cytoplasmic CD3, CD4, variable CD9, strong CD7, strong CD13, CD30 and HLA-DR (66%). There is no expression of surface CD3, CD5, CD8, CD10, CD11b, CD11c, CD14, CD16, CD19, CD20, CD33, CD34, CD36, CD57, CD64, CD79a, CD117, CD123, CD303, CD304, myeloperoxidase nor TDT.
Bone marrow aspirate clot preparation: The atypical cells express CD7 with variable de-regulation of CD2, CD3 and CD7 expression resulting in variable positivity with these antibodies. They are predominantly CD4+ with only occasional CD8+ neoplastic cells and also show variable positivity with CD25, granzyme B, CD56, CD99, CD68P and CD20 antibodies. MIB-1 is positive in virtually all of the neoplastic cells as is CD30 and ALK.
Bone marrow trephine: Inadequate sample with rare CD30+ and ALK+ cells.
Cytogenetics: 31% Positive for ALK (2p23) rearrangement.
Molecular studies: None
Proposed diagnosis: ALK+ anaplastic large cell lymphoma.
Interesting feature(s) of submitted case: The patient was critically unwell and a rapid diagnosis was required. Given the clinical urgency, a clot preparation was used to rapidly confirm the presence of ALK+/CD30+ neoplastic cells, confirming the diagnosis of anaplastic large cell lymphoma. This was later confirmed by FISH.

EAHP18-BMWS-408

Primary bone marrow presentation of peripheral T cell lymphoma, not otherwise specified, in a pediatric patient

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Case description: A 13-year-old boy with no significant past medical history presents with 2-month history of upper respiratory symptoms, fatigue, fevers, night sweats and lower extremity pain. Physical exam showed no lymphadenopathy or hepatosplenomegaly. CBC shoes pancytopenia (WBC 1.2 x 10^9/L, Hgb 7.7g/dL, and PLT 78 x 10^{9}/L, ANC of 150/ul). Chest X-ray was normal. PET-CT scan showed extensive signal in the bones and small foci in left axillary and inguinal lymph nodes. The patient was admitted to the Children's Hospital of Philadelphia and underwent bone marrow studies.

Biopsy fixation details: Formical 2000 and AZF followed by formalin.
Frozen tissue available: None
Details of microscopic findings: H&E stained sections show hypercellular bone marrow for age (>90%) with reduced trilineage hematopoiesis and sheets (60-70% of cellularity) of variably sized mononuclear cells with irregular nuclei, vesicular chromatin, occasional nucleoli and small amount of pink cytoplasm. Bone marrow sinuses are dilated.
Immunophenotype: Immunohistochemical stains performed on the biopsy core show that the atypical cells are positive for CD3, CD2, CD8 with loss of CD5 and CD7. They are also negative for CD30, ALK1 and EBER(ish). Flow cytometry performed on the bone marrow aspirate show abnormal T-cell population with increased CD2 and CD38, decreased CD8, normal CD3 and CD45, and absence of CD5 and CD7.
Cytogenetics: Cytogenetic studies show an abnormal male karyotype: 49,XY,add(9)(p?24),+12,+14,+20[13]/98,idemx2,add(8)(q24)x2[4]/46,XY[7].
Molecular studies: Comprehensive NGS hematologic mutation studies for ~100 SNVs and Indels were negative. Fusion studies (Archer Fusionplex) were negative.
Proposed diagnosis: Peripheral T-cell lymphoma, not otherwise specified, involving bone marrow.
Interesting feature(s) of submitted case: Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), with extensive bone marrow involvement.
PTCL-NOS in children is extremely rare and frequently presents with high stage disease and marrow involvement.
Prognosis in children with marrow disease is poor, and the patient succumbed to this disease less than 1 year after initial diagnosis despite aggressive therapy.

EAHP18-BMWS-424

CD30+ T cell lymphoma with bone marrow presentation and hemophagocytic lymphohistiocytosis

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Case description: A 69-year-old male presented to the ER complaining of dizziness, coughing, shortness of breath, abdominal pain, cramping and diarrhea for 1-2 weeks. Clinical history included hypertension, coronary artery disease (recent bypass 6 months prior), GI bleed, reflux, Sjogren syndrome, nephrectomy for carcinoma 6 years ago and knee surgery. Admitted to ICU for sepsis workup due to severe leukopenia and fever (40.5ºC). Cultures and serology were negative but persistent high fever led to working diagnosis of hemophagocytic syndrome/lymphohistiocytosis (HPS/HLH).
Bone marrow biopsy (BMB) elsewhere reportedly with a hypocellular marrow and no evidence of HP and a differential of low-grade myelodysplastic syndrome vs myelotoxicity. Pan-cultures were negative and BMB performed 9 days after the first sample. LABS with increased LAP, ALT, AST, LDH (6810), PT, ferritin (16,000), D-dimer (>20), hypofibrinogenemia and hypoalbuminemia. CBC showed pancytopenia: HGB 10.9, WBC 0.1, PLT 52. CT negative for organomegaly; retroperitoneal and mediastinal increased number of normal-sized lymph nodes.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: N/A
Details of microscopic findings: Hypocellular BM with decreased granulocytic and erythroid precursors, dyspoietic megakaryocytes, stromal injury and rare interstitial atypical cells, medium to large size, with ovoid nuclei, variably condensed chromatin, occasional prominent large eosinophilic central nucleoli and abundant cytoplasm, and rare Reed-Sternberg–like cells. No lymphoid aggregates or fibrosis. Touch imprints show tumor cells with large or medium-sized hyperchromatic nuclei and large central nucleoli, abundant basophilic cytoplasm with eosinophilic granules. Peripheral blood shows pancytopenia with severe neutropenia, rare Döhle bodies and no circulating tumor cells.
Immunophenotype: IHC: tumor cells expressed CD30 (strong, diffuse, membranous and Golgi pattern), CD3, CD7 (weak, subset), CD45, CD8 (small subset), Beta F1 (weak), EMA (subset), TIA-1, Granzyme B, perforin and are negative for CD5, CD15, CD20, CD34, CD123, TDT, ALK1, PAX5, CD68, EBV-LMP and EBER. No sinusoidal pattern. CD68+ histiocytes increased, only rare cells with hemophagocytosis. FCM:abnormal population with CD2, CD3, CD7, CD8, CD30, CD45bright, CD45RA, and negative for CD4, CD5, CD13, CD16, CD33, CD34, CD56 and CD57. Review of earlier BMB showed interval decreased cellularity and presence of CD30+ lymphoma cells in the first sample.
Cytogenetics: 47,XY,+6[5]/46,XY[1]. FISH with ALK break-apart probe-negative.
Molecular studies: T cell gamma receptor clonal rearrangement by PCR; B cell clonality negative.
Proposed diagnosis: CD30+ T cell lymphoma, favor ALK- ALCL involving marrow at presentation with HLH
Interesting feature(s) of submitted case: Secondary HLH with rapid onset pancytopenia can mimic acute leukemia clinically and hypoplastic MDS histologically.The HP histiocytes may be rare or absent likely due to BM depletion and underlying T-cell lymphoma in HLH can be subtle and overlooked. Only approximately 7% of ALK-ALCL involve bone marrow (1) usually late in the course of the disease. ALK- ALCL with leukemic presentation is rare (2-4) and medullary presentation associated with HLH exceptional (5).

1. Savage KJ et al. Blood 2008;111: 5496-5504
2. Lu Y et al Leuk Res. 2010 ;34:475-82
3. Tanaka H et al. Intern Med. 2012;51:199-203
4. Wong WS et al. Leuk Lymphoma. 2010;51:1927-30
5. Xu Z, Burns BF. Hemophagocytosis due to bone marrow ALCL, ALK–. Blood. 2014 24;12:478.

EAHP18-BMWS-480

Leukemic phase of anaplastic large cell lymphoma in a 1-year-old child who received stem cell transplant for presumed hemophagocytic lymphohistiocytosis

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Case description: A male infant presented at 5 months of age with symptoms and laboratory abnormalities compatible with hemophagocytic lymphohistiocytosis (HLH). He initially responded to the treatment per HLH-2004 protocol but relapsed at 9 months of age. He then received unrelated donor (URD) matched stem cell transplant (SCT) at 13 months of age. He presented on Day 29 post SCT with fever, running nose, cough, and diarrhea. Physical examination did not reveal significant lymphadenopathy (LAD). CBC revealed marked anemia, thrombocytopenia and atypical lymphocytes. Graft-versus-host disease (GVHD) or post-transplant lymphoproliferative disorder (PTLD) were suspected.
Biopsy fixation details: Bone marrow aspiration and sigmoid colonoscopy-guided biopsy were performed. Wright-Giemsa stains were performed on peripheral blood and marrow aspirate smears. Colon biopsy was fixed in formalin.
Frozen tissue available: None
Details of microscopic findings: The peripheral blood smears revealed frequent atypical lymphocytes, which were medium-sized, containing minimal basophilic cytoplasm with vacuoles, oval to slightly convoluted nuclei, partially clumped chromatin, and inconspicuous nucleoli.
The bone marrow aspirate smears demonstrated partially preserved progressive multilineage hematopoiesis, and many atypical cells morphologically like those observed in peripheral blood.
Colon biopsy revealed atypical lymphocytic infiltrate involving lamina propria and submucosa, with focally nodular pattern. The infiltrating cells were medium to large, with minimal cytoplasm, oval hyperplastic nuclei, and inconspicuous nucleoli. Numerous apoptotic bodies and patchy necrosis were also seen.
Immunophenotype: Flow cytometric analysis of the marrow aspirate revealed that approximately 21% of marrow cells are immunophenotypically abnormal T cells expressing CD45, cytoplasmic CD3, aberrant CD13, positive for
HLA-DR, CD2 (partial), CD7, negative for surface CD3, CD34, TdT, CD5, CD4, CD8, CD10, CD34, CD1a, CD99, CD56, CD19, MPO, CD14, CD117, and CD33.
IHC stains of the colon biopsy showed that the atypical cells were positive for CD3, strongly positive for CD30 and ALK, negative for CD5.
Cytogenetics: Abnormal mosaic male karyotype
donor 46,XX[3]
clone 1 46,XY,t(2;5)(p23;q35.1),t(3;11)(p13;q25),t(8;15)(q24.1;q22)[17]
FISH with break apart probes was positive for ALK-1 translocation.
Molecular studies: None
Proposed diagnosis: Anaplastic large cell lymphoma, ALK-positive, small cell variant, presenting with pure leukemic phase
Interesting feature(s) of submitted case: Anaplastic large cell lymphoma (ALCL), ALK-positive commonly presents with lymphadenopathy or extranodal mass lesions, although leukemic phase of ALCL, usually associated with small cell morphology and with or without concurrent lymph node or tissue involvement, has been rarely reported.
Diagnosis of purely leukemic phase of ALCL is challenging, because the circulating lymphoma cells may morphologically resemble reactive lymphocytes. The immunophenotype of these lymphoma cells may also mimic T-lymphoblastic lymphoma.
ALCL has been reported to be associated with hemophagocytic lymphohistiocytosis (HLH), which may mask the lymphoma and leads to an incorrect diagnosis and thus inappropriate management.
Our case has the following peculiar features: purely leukemic phase presentation at very young age; initial misdiagnosis as HLH and management as such; quickly relapsed disease post SCT. Recognition of this unusual presentation of ALCL will promote timely and accurate diagnosis and ensure proper management of disease.

EAHP18-BMWS-482

A case of angioimmunoblastic lymphoma presented in the bone marrow

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Case description: Clinical History
The patient is an 89 years female with RA developed cytopenia and got the diagnosis of myelodysplastic syndrome RCMD for 6 years before. Received only supportive care and she subsequently came to our university hospital with complaints of weight loss, itching and fatigue. LAB: peripheral blood HB 103 g/l, hypereosinophilia and lymphocytosis. An enlarged node could be found in the axilla. Fine needle aspiration revealed normal morphology and the flow cytometric analysis shows normal phenotype.
Biopsy fixation details: Bone marrow core needle biopsy material, formalin fixed for paraffin embedded. Bone marrow aspirate and peripheral blood smears submitted. Additionally, provided bone marrow aspirate in EDTA for flow cytometry and molecular studies.
Frozen tissue available: Not available.
Details of microscopic findings: The peripheral blood smear apparent lymphocytosis and eosinophilia. Unfortunately showed the BM smear the same findings as in the peripheral blood telling for blood-mixed material. However, the bone marrow core biopsy was representative and extremely hypercellular, showed multilinear dysplasia but no blast increase. Additionally, showed multiple not well defined demarcated small lymphocytes infiltrates.
Immunophenotype: Immunhistochemical stains: The lymphoid infiltration is dominated by T cells positive for CD3. In the infiltrate there is an apparent dominance of CD4 positive. T cells were strongly positive for ICOS and PD1. Furtherly beta-F1+, a subpopulation CXCL13+, no loss of CD2, CD5 or CD7. BCL6 variable. Stain for EBER ISH shows within infiltrates a few positive cells. Flow cytometry analysis on the bone marrow: T cells exhibit normal phenotype and CD4 / CD8 ratio of 2.1. However, identified a clear fraction of small lymphocytes, positive for CD45, CD5, CD4, CD2, CD28, CD45RO, CD27, CD52, mostly positive for CD7, with heterogeneous expression of HLA-DR and partial positivity for CD10. These are positive for cytoplasmic CD3 but negative for membrane CD3, CD56, CD26, CCR7, CD26, CD57, CD45RA, Tdt, CD1α and B cell markers. Furthermore, another discrete deviating lymphocyte fraction (CD45 + CD56 + CD3-CD4-CD8-CD2-CD5-CD7-CD16- is detected. Otherwise, in the T cell population, the dominance of CD45RO positive memory T cells is noted. Cytotoxic T cells with LGL-like phenotype make up only 0.2% of total. NK cell population is sparse and show ordinary phenotype.
Cytogenetics: Chromosome analysis showed normal karyotype. FISH analysis performed on interphase cells of bone marrow smear regarding eosinophil panel ABL 9q34 SO/BCR 22q11.2 SG DF 408 and revealed normal results.
Molecular studies: PCR analysis showed that in bone marrow aspiration, the T cells are clonal, with rearrangement of TCR gamma and TCR beta genes.
Proposed diagnosis: The findings are consistent with bone marrow engagement and leukeumiserad to peripheral T-cell lymphoma. The phenotype suggests follicular helper T cell phenotype (FTH) and is reminiscent of angio-immunoblastic T cell lymphoma.
DD Peripheral T-cell lymphoma, not otherwise specific
Interesting feature(s) of submitted case: Elderly patient with MDS who received only conservative treatment presented with allergic manifestations and weight loss as typical clinical features for angio-immunoblastic lymphoma. There are few EBER positive cells, but it is not enough to consider it as an EBV- driven.

EAHP18-BMWS-491

CD4-positive T-cell leukemia involving bone marrow and peripheral blood: a case of indolent T-cell prolymphocytic leukemia or an underappreciated entity?

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Case description: A 73-year-old man had persistent leukocytosis for 3.5 years, first detected in 2014 with a white cell count (WBC) of $16x10^9$/L. His WBC steadily increased to $21x10^9$/L in 2015 and $53x10^9$/L in 2016. The patient had no symptoms and was observed. He was referred to our institution in 2018 with a WBC count of $65x10^9$/L including 93% of lymphocytes. There were mild anemia (hemoglobin 13.3g/dL) and thrombocytopenia (platelet 107 $x10^9$/L). No skin lesions, lymphoadenopathy or splenomegaly were present and he had no other symptoms. Bone marrow aspiration and biopsy were performed at our hospital.
Biopsy fixation details: Fresh tissue submitted for ancillary studies; formalin fixed tissue submitted for morphologic evaluation and immunohistochemical studies.
Frozen tissue available: No
Details of microscopic findings: Both peripheral blood and bone marrow smears showed an abnormal lymphocytic population composed of small to medium-sized lymphocytes with slightly irregular nuclei, variably dispersed to condensed chromatin and small amounts of basophilic cytoplasm with no visible granules. Occasional cells had small but conspicuous nucleoli and rare cells showed cytoplasmic blebs. Bone marrow biopsy showed an atypical lymphoid infiltrate in a diffuse and interstitial pattern involving 70% of bone marrow cells. The infiltrate was composed of medium sized lymphocytes with irregular nuclei.
Immunophenotype: Flow cytometry showed a T-cell population positive for CD2, CD3 (surface), CD4, CD5 (bright), CD7, CD25 (partial), CD45, CD52 (bright) and T-cell receptor (TCR) alpha/beta, and negative for CD8, CD10, CD16, CD26, CD30, CD56, CD57, CD94 and TCR gamma/delta. By immunohistochemistry, the neoplastic T-cells were positive for CD3 and negative for TCL1, CD1a, CD25, CD34, TdT and TP53. In situ hybridization for EBER1 was negative.
Cytogenetics: The conventional cytogenetics showed a complex karyotype without the abnormalities in regions including 14q32 and Xq28 (see ppt file). Fluorescence in situ hybridization (FISH) studies using a TCL1 dual color, breakapart probe showed no TCL1 rearrangement.
Molecular studies: Monoclonal TRG and TRB gene rearrangements were detected by PCR analysis. Next generation sequencing-based analysis for somatic mutations in a total of 81 genes was performed. JAK1, JAK3 and STAT5B were included in this panel and no mutations were detected.
Proposed diagnosis: CD4-positive T-cell leukemia
Interesting feature(s) of submitted case: The overall findings are diagnostic of a CD4-positive T-cell leukemia. The subclassification of this neoplasm, however, is challenging. An indolent T-cell prolymphocytic leukemia (T-PLL) was considered. Although most T-PLL patients present with an aggressive clinical course with hepatosplenomegaly and generalized lymphadenopathy, occasional cases with a relatively indolent clinical behavior had been reported in the literature and a few of them have had a complex karyotype. Features not consistent with classic T-PLL in this case included: 1), the absence of TCL1 rearrangement or TCL1 protein expression, which is seen in 90% of T-PLL cases; 2), absence of other cytogenetic abnormalities commonly associated with TCL1-negative T-PLL such as t(X;14), and 3), absence of mutations in the JAK-STAT pathway (JAK1, JAK3, STAT5B) that are present in about 70% of cases. In addition, the neoplastic cells were negative for CD26 in contrast to bright CD26 in most T-PLL cases. This case highlights the heterogeneity within the current definition of T-PLL and suggests that neoplasms such as this case may represent a distinct, underappreciated entity.

EAHP18-BMWS-502

Primary bone marrow presentation of ALK-negative anaplastic large cell lymphoma with hemophagocytic syndrome

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Case description: 52 year-old Caucasian male with clinical picture suggestive of acute cholecystitis (fever, elevated PCR, ferritin, AST/ALT and GGT levels). Chest and abdominal CT scan revealed mild hepatomegaly with pericholecystic effusion. No abdominal and/or thoracic lymphadenopathies were noted. Based on the putative diagnosisis of cholecystitis, the patient underwent laparoscopic cholecystectomy, which was followed by acute respiratory failure, progressive anaemia, thrombocythopaenia and lymphopenia. The results of bone marrow (BM) evaluation (see below) prompetd the administration of high dose (CHOEP and ICE) chemotherapy, with only transient response. Relapsed disease was treated with Brentuximab-vedotin with short-term remission. Seven months after diagnosis the patient died of disease.
Biopsy fixation details: The biopsy was fixed in formalin.
Frozen tissue available: n.a.
Details of microscopic findings: Morphological evaluation disclosed a hypercellular (80%) BM with maturing trilinear hematopoiesis and slightly increased megakaryopoiesis, with occasional atypical forms. Hemophagocytic histiocytes were scattered thought the intertrabecular spaces. An interstitial lymphoid infiltrate was also present, which mainly consisted of large atypical blasts with irregular nuclei. Discrete numbers of accompanying mature T-cells were also found. The atypical lymphoid infiltrate was heterogeneously distributed in the intertrabecular spaces, varying from 15% to 50-60% of BM cellularity. Reticulin stain did not show any evidence of interstitial fibrosis.
Immunophenotype: The atypical lymphoid cells were positive for CD30, Perforin, EMA, CD43, CD2 and consistently negative for CD3, CD5, CD7, CD4, CD8, Granzyme B, TIA1 and CD20. Flow cytometry confirmed the immunohistochemical results, also disclosing positivity for CD25.
Cytogenetics: n.a.
Molecular studies: n.a.
Proposed diagnosis: Bone marrow infiltration of CD30-positive T-cell lymphoma with features of ALK-negative anaplastic large cell lymphoma, associated with hemophagocytic syndrome.
Interesting feature(s) of submitted case: This unusual CD30-positive T cell lymphoma is characterized by primary BM presentation, with no evidence of mass-forming (nodal and/or extranodal) lesions. Of note, careful histological examination of the gall bladder specimen after BM evaluation disclosed tumor micro-emboli in the pericholecystic vessels. A pericholechystic lymph node (main diameter: 0.6 cm) also disclosed partial sub-capsular and sinus infiltration of CD30-positive large T cells akin to those observed in the BM. These latter findings confirmed the prior diagnosis of lymphoma and may contribute to explain the clinical presentation closely mimicking acute cholecystitis.
The morphology and phenotype of the neoplastic cells suggest the differential diagnosis between ALK-negative anaplastic large cell lymphoma (ALCL) and CD30-positive peripheral T-cell lymphoma, not otherwise specified. Such a differential diagnosis can be very challenging in the BM. In the present case, however, the large size and atypical morphology of the neoplastic cells, the strong and diffuse positvity for CD30, the defective cytotoxic phenotype and the sub-capsular/intra-sinus nodal growth pattern strongly favor the diagnosis of ALK-negative ALCL. Finally, hemophagocytic syndrome is a well–known complication of peripheral T-cell lymphomas and its occurence should always prompt careful histological and/or cytological evaluation for BM neoplastic lymphoid infiltrates.

EAHP18-BMWS-520

BONE MARROW INVOLVEMENT IN A CASE OF ADULT T-CELL LEUKEMIA/LYMPHOMA

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Case description: A 38 year-old female with a history of erythematous pruritic eruptions with generalized distribution (2014), presented with alteration of the general state, fever, splenomegaly. Clinical examination revealed multiple superficial lymphadenopathy in the both sides of the neck, axilla, inguinal region (measuring 1.5/2,0 cm). Peripheral blood findings showed leukocytosis (123.450/mm3), normal hemoglobin and thrombocytopenia (63.000/mm3). Biochemical tests yielded hepatic cytolysis with cholestasis while the ionogram revealed hypercalcemia. Serological analysis revealed the presence of HTLV-1 antibodies.
The patient was submitted to 7 x CHOP regiment and to a second line of with GIFOX (gemcitabine, ifosfamide, oxaliplatin) with poor response and relapses between each cycle. During the follow-up, the disease progressed rapidly, with extensive lymphadenopathy, neurological manifestations (hemiparesis, dysarthria), pulmonary micronodules and soft tissue involvement. Her condition deteriorated progressively and she died 11 months after the initial presentation.
Biopsy fixation details: 10% buffered formaldehyde fixation and Na2EDTA decalcification
Frozen tissue available: peripheral blood and marrow aspirate
Details of microscopic findings: Bone marrow biopsy: The BMB is hypercellular (~90 cellular component), showing patchy and interstitial infiltration of malignant lymphoid cells (~50-55%) with polimorphous medium-sized cells, cleaved nuclei, fine chromatin and inconspicuous nucleoli admixed with areas of conserved hematopoiesis, with trilineage maturation present in a slightly decreased number.
Myelogram appeared to be normocellular, ~ 13-15% polymorphous lymphocytes with round nuclei and mildly condensed chromatin; hypocellular granulocytic series (45-46%) with maintained maturation, presence of large (gigantocyte) and isolated hypogranular granulocytes; increased erythropoiesis of normoblast type (36-37%) with frequent megaloblastoid features and mild dyserythropoiesis; hypercellular megakaryocytic series with maintained maturation
Immunophenotype: Immunohistochemistry on BMB: The tumor cells were mature T-lymphocyte, positive for CD3 and CD5 but they lost the CD7 expression, with a helper phenotype, CD4+CD8-; the malignant cells were positive for CD25; the malignant proliferation was negative for CD20, CD30 and Granzyme B.
Immunophenotypic analysis of peripheral blood and bone marrow aspirate was performed with Navios Flow Cytometer on 100000 events, analyzed with Kaluza software, and revealed a cellular population (70% on peripheral blood, 25% on marrow aspirate) positive for CD45+, SSC low, with the following phenotype: icCD3+, sCD3-, CD25+, CD2+ (mild expression), CD5+, CD4+, CD38+ and negative for the remaining antibodies tested.
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: The clinical, histopathological, immunohistochemical and flow cytometry findings are consistent with the diagnosis of HTLV-1 induced adult T-cell leukemia (ATL).
Interesting feature(s) of submitted case: ATLL is a distinct subtype of T-cell lymphoma etiologically related to human T-cell lymphotropic virus type-1 (HTLV-1) infection, which is endemic in several regions of the world. In Europe, Romania seems to be the only country with an endemic region, having a high HTLV-1 prevalence (over 1/10 000 among first-time blood donors). The epidemiologic data explain why the ATLL is the second most common malignant T cell lymphoproliferative disorder in Romania, after PTCL NOS.

EAHP18-BMWS-535

CD4+/TCRαβ+ hepatosplenic T-cell lymphoma with primary bone marrow presentation

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Case description:
A previously healthy young man, 18 years old, presented with several weeks history of fatigue. Laboratory findings at presentation included severe pancytopenia (Hb 71 g/L, leukocytes 0,5 x 10^9/L, platelets <5 x 10^9/L and elevated LD (23)). Physical and radiologic examination revealed hepatosplenomegalia but no lymphadenopathy. Subsequent bone marrow examination (dry tap) revealed a T-cell lymphoma in the bone marrow biopsy as determined by morphology, immunophenotyping and monoclonal TCR gene rearrangements. A small T-cell lymphoma population (1%) in the peripheral blood was also found at diagnosis as judged by flow cytometry. The patient was treated with chemotherapy (CHOEP, etoposide) and basiliximab, but relapsed 3 months later with 28% lymphoma cells in the peripheral blood and eventually succumbed to his disease one month after the relapse. He never displayed peripheral blood without evidence of disease during or after treatment.
Biopsy fixation details:
4% formaldehyde.
Frozen tissue available:
Not available.
Details of microscopic findings:
In the peripheral blood, a few atypical lymphocytes were observed. In the bone marrow imprints, a promiment population of atypical lymphocytes with medium-sized lymphocytes with irregular nuclei and moderate bluish cytoplasm was seen. The bone marrow biospy revealed a cellularity of 100%, moderate reticulin fibrosis, and a diffuse infiltration of T-cell lymphoma cells without obvious sinusoidal infiltration. Erythroid cells were scarce, megakaryocytes were increased with reactive changes, and granulopoesis was reduced and slightly left-shifted.
Immunophenotype:
The lymphoma cells were CD2++/CD3+/CD5-/CD4+/CD8-/CD7-/CD16-/CD26-/TCRαβ+/CD30-/CD25(+)/CD52-/CD56(+)/CD57-/EBER-/TIA1(+)/granzymB- as determined by flow cytometric analysis of peripheral blood and immunohistochemistry on the bone marrow biopsy
Cytogenetics:
Not determined because of the dry tap and few mitoses.
Molecular studies:
Monoclonal rearrangements of TCR-beta and -gamma. Massive parallel sequencing (Illumina myeloid panel) revealed a mutation in TET2 in 24% of the reads.
Proposed diagnosis:
Hepatosplenic CD4+/TCRαβ+ T-cell lymphoma.
Interesting feature(s) of submitted case:
Unusual variant of hepatosplenic T-cell lymphoma with expression of both TCRαβ and CD4. Significance of TET-mutation?

EAHP18-BMWS-566

Breast implant-associated anaplastic large cell lymphoma with extensive bone marrow involvement

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Case description: A 58 year-old woman presented with firmness of the left breast. Mammogram of the breast from showed a 3.2 x 5.5 cm cystic breast lesion and a left axillary mass with no other suspicious axillary, infraclavicular or internal mammary lymphadenopathy. She endorsed a history of cosmetic breast implants placed approximately 20 years prior to this presentation. A PET-CT study showed multifocal hypermetabolic osseous lesions. Excision and histologic examination of the left breast implant capsule confirmed a diagnosis breast implant associated anaplastic large cell lymphoma.
Biopsy fixation details: Bone marrow (BM) aspiration (unfixed) and core biopsy and clot specimen (formalin fixed paraffin embedded tissue, core decalcified using formic acid).
Frozen tissue available: No
Details of microscopic findings: The bone marrow core biopsy and clot section were hypercellular for age. The bone marrow clot showed an extensive infiltrate of large, atypical cells forming sheets and involving ~60% of bone marrow cellularity. Occasional neoplastic cells had horseshoe-like nuclei but many exhibited spindle-shaped morphology. Mitotic figures, including atypical forms, and apoptotic cells were readily identifiable. The background bone marrow showed eosinophilia and mildly increased plasma cells. The bone marrow core biopsy showed only a focal, perivascular cluster of atypical cells.
The bone marrow aspirate smears showed frequent large, highly atypical cells with high nuclear:cytoplasmic ratio, folded, horseshoe or spindle-shaped nuclei, prominent nucleoli and scant eccentric cytoplasm, often imparting a tadpole-like appearance.
Immunophenotype: Immunohistochemical studies performed on sections of the bone marrow clot showed the neoplastic cells were positive for CD30 (strong, uniform), CD43, and CD4, and negative for CD3, CD20, CD45/LCA, ALK-1, CD8, HHV8, and pancytokeratin.
Flow cytometric analysis of a concurrent bone marrow aspirate sample identified an aberrant T cell population with the following immunophenotype: CD2(+), CD3(-), CD4(dim+), CD5(-), CD7(-), CD8(-), CD10(-), CD16(-), CD25(bright+), CD26(subset+), CD30(bright+), CD52(+), CD56(-), CD57(-), CD94(-), TCR-AB(-), and TCR-GD(-).
Cytogenetics: GTL banded karyotype using unstimulated and LPS-stimulated bone marrow cultures: 51,XX,+2,+add(6)(p21.3),der(12)t(1;12)(q21;q24.3),+21,+2mar[3]/46,XX[17]
Molecular studies: Not done.
Proposed diagnosis: Breast implant-associated anaplastic large cell lymphoma extensively involving bone marrow.
Interesting feature(s) of submitted case: Systemic involvement by breast implant associated ALCL is exceedingly rare and bone marrow involvement has not been previously reported. This case presented a diagnostic challenge because the patient had a very unusual presentation with multifocal bone and bone marrow involvement. Recognition of this pattern of involvement in patients with breast implant associated ALCL is critical for accurate diagnosis and appropriate patient management.

EAHP18-BMWS-126

Classic Hodgkin lymphoma presenting with bone marrow involvement, initially mis-diagnosed as chronic eosinophilic leukemia

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Case description: The patient is an 80 year old man with a 13 year history of follicular lymphoma (FL). In 2015 he presented with new symptoms including fatigue, pruritus, and mildly elevated LDH of 231. Lymph node biopsy of a prominent node showed FL, grade 3A. He was treated on a clinical trial with lenalidomide and rituximab and had a partial response with regard to his lymphadenopathy. However, he continued to have pruritus and fatigue, but denied fevers, night sweats or weight loss. CBC at this time revealed a WBC of 17.7 x 10^9/L with 74% eosinophils and anemia (Hgb 8.8 g/dL).
A bone marrow (BM) biopsy was performed to evaluate for the etiology of the eosinophilia, and showed a normocellular marrow with increased eosinophils and no definitive features of mastocytosis or lymphoma. Tryptase stain, PDGFRA FISH, T-cell flow cytometry and chromosomes were normal. Next generation sequencing (NGS) showed a KIT: c.1621A>c; pMet541Leu mutation at 51% VAF. Although this variant is most often a benign polymorphism, it has been reported in a group of patients with chronic eosinophilic leukemia, NOS who responded to imatinib (reference).
Based on these results and lack of other causes of his eosinophilia, he was treated with prednisone and imatinib, but had persistent eosinophilia, pruritus, and fatigue. CT scans at this time showed stable, diffuse lymphadenopathy; unchanged from prior scans with the largest node measuring 2.1 cm. Spleen appeared normal. Imatinib was discontinued. BM was repeated and demonstrated extensive replacement by classic Hodgkin lymphoma.
Biopsy fixation details: B5/decalcification
Frozen tissue available: no
Details of microscopic findings: Extensive marrow replacement by a mixed inflammatory infiltrate including histiocytes, eosinophils, and small lymphocytes with admixed Reed-Sternberg cells and variants.
Immunophenotype: RS cells express CD30, Pax5. Negative for CD45, CD25, CD20, ALK, CD3 and EBV-ISH.
Cytogenetics: 46, XY
Molecular studies: KIT: c.1621A>c; pMet541Leu (51% VAF)
Proposed diagnosis: Classical Hodgkin lymphoma extensively involving bone marrow.
KIT M541L mutation, likely benign variant
Interesting feature(s) of submitted case: This is a dramatic example of a patient who presented with bone marrow-based classic Hodgkin lymphoma (CHL). There were several red-herrings in this case which obscured the diagnosis of CHL including the patient's prior diagnosis of follicular lymphoma which accounted for much, if not all, of his lymphadenopathy at the time of presentation. The eosinophilia and pruritus are typical features of CHL, but a lymph node biopsy showing follicular lymphoma, and a negative initial bone marrow exam led the clinical team to consider other etiologies for the eosinophilia. When NGS revealed a KIT mutation, which has been described in a small group of patients with CEL, NOS, this created yet another diversion from the true diagnosis. It was only after the patient failed to respond to a course of imatinib, that the clinicians repeated the bone marrow and revealed extensive involvement by CHL.
In summary, this case highlights potential pitfalls of CHL when it presents primarily with bone marrow-based disease. It is likely that the lymphoma was missed on the initial BM exam due to sampling error/patchy disease. This case also highlights a pitfall of performing NGS testing in the absence of a definitive neoplastic infiltrate, as this can lead to results which, not only may be of uncertain clinical significance, but may ultimately distract from the true diagnosis.
Reference: Lurlo et al. Oncotarget. 2014 Jul 15;5(13):4665-70.

EAHP18-BMWS-150

Classic Hodgkin lymphoma involving bone marrow as primary presentation

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Case description: The patient is a 13-year-old male with no past medical history who presented with at least 2-month history of persistent fevers, pallor, and decreased appetite. At presentation, laboratory studies showed Hgb of 5.9 g/dL (with normal white blood cells and platelet counts). The patient was admitted for anemia and additional work up indicated increased LDH >1500 (normal 165-310 units/L), mildly elevated liver enzymes and uric acid of 6 (normal 2.3-8.6 mg/dl). Chest CXR was unremarkable. The patient had elevated ESR and CRP, and positive DAT with anti-C3 and anti-IgG consistent with warm autoimmune hemolytic anemia. Hematology service was consulted and bone marrow evaluation was recommended prior initiating treatment with steroids for the presumed diagnosis of autoimmune hemolytic anemia in order to exclude malignancy. Preliminary bone marrow findings indicated infiltrating process (leukemia was excluded). Subsequent PET/CT studies showed extensive nodal disease predominantly in the abdomen and pelvis, but also involving the right paratracheal and right mediastinal areas. There was diffuse hypermetabolic foci within the enlarged spleen, and the liver was diffusely hypermetabolic as well. There were numerous sites of abnormal osseous uptake.
Biopsy fixation details: The biopsy of the bone marrow was from the left posterior iliac crest. The core biopsy was fixed with 10% neutral buffered formaldehyde prior to further processing.
Frozen tissue available: Not performed.
Details of microscopic findings: The bone marrow aspirate was aspiculate, hemodiluted with mostly peripheral blood components, and inadequate for evaluation. The left core biopsy specimen was adequate in size and composed of cortical and trabecular bone with an extensive diffuse infiltrate that showed fibrosis and mixed inflammatory background (composed of small lymphocytes, histiocytes and occasional eosinophils and plasma cells) with scattered atypical large cells. The large cells had a prominent nuclear membrane and an eosinophilic nucleolus, resembling Reed-Sternberg or Hodgkin cells. No normal marrow with trilineage hematopoiesis was present.
Immunophenotype: Bone marrow immunohistochemistry showed that the large tumor cells were positive for CD30 and CD15, while they were negative for CD45, CD3, CD20, CD42b, CD61, CD34, and CD117. The PAX5 highlighted a small number of small lymphocytes, while focally a few of the tumor cells were weakly positive. In situ hybridization for EBV small encoded RNA (EBER) was positive in the large tumor cells.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Classic Hodgkin lymphoma (primary bone marrow site presentation).
Interesting feature(s) of submitted case: Involvement of bone marrow by classic Hodgkin lymphoma is rare (3%) and usually is recognized at staging in patients with an established diagnosis of Hodgkin lymphoma in an extramedullary site. The bone marrow may also be the initial site of diagnosis in patients who undergo bone marrow examination for unexplained cytopenias. In this case, the patient presented with significant anemia and laboratory findings consistent with autoimmune hemolytic anemia (AIHA). Although infrequent, AIHA can be responsible for the presenting symptom in Hodgkin lymphoma. Establishing a primary diagnosis of Hodgkin lymphoma in a bone marrow specimen can be challenging and requires the identification of diagnostic Reed-Sternberg cells in an appropriate cellular environment characteristic of Hodgkin lymphoma.

EAHP18-BMWS-191

Classical Hodgkin lymphoma presenting in the marrow of a 26-year-old man with history of rheumatoid arthritis treated with methotrexate.

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Case description: The patient was a 26-year-old man with 6-year history of rheumatoid arthritis (RA) on methotrexate (MTX). In 10/2011, he presented with 20 lb weight loss, fatigue, night sweats and chills. In 02/2012, anemia developed (hemoglobin:7.5 g/dL). MTX was suspended but anemia persisted. Imaging showed liver cirrhosis, splenomegaly (17 cm) and borderline enlarged aortic lymph nodes (1.5 cm max). A bone marrow biopsy (BMB) in 03/2012 showed marked fibrosis and was considered suggestive of autoimmune or toxic myelofibrosis. Prednisone and rituximab provided only subjective improvement. In 12/2012, a second BMB showed persistent fibrosis, eosinophilia and involvement by classical Hodgkin lymphoma (CHL). Clinical remission was obtained with ABVD and blood counts improved. In 06/2015, the patient was still clinically free from lymphoma but developed pancytopenia. He was diagnosed with therapy-related myelodysplastic syndrome (t-MDS), progressed to AML in 01/2016 and died in 04/2016.
Biopsy fixation details: Bone marrow cores were fixed in B+ fixative and decalcified with Rapid Cal solution.
Frozen tissue available: No.
Details of microscopic findings: BMB, 03/2012: Cellularity 20-30% with decreased maturing trilineage hematopoiesis and abundant interstitial plasma cells, lymphocytes and eosinophils in a fibrotic background (WHO grade MF-2). No diagnostic Reed-Sternberg cells are recognized.
BMB, 12/2012: Cellularity 50% with marked myeloid hyperplasia, eosinophilia, left-shifted erythroid maturation and persistent fibrosis (MF-2). Also present are several non-paratrabecular aggregates and an interstitial infiltrate of small and occasionally large lymphoid cells with round to irregular nuclei. A CD25 stain performed to evaluate for the possibility of mastocytosis, stained scattered large, occasionally binucleated cells with prominent nucleoli, that were difficult to appreciate on routine histology. Additional stains (see below) confirmed these to be Reed-Sternberg cells.
Following the diagnosis of marrow involvement by CHL in this biopsy, careful review of additional recuts and immunostains of the 03/2012 BMB showed very rare large, atypical cells consistent with Reed-Sternberg cells.
BMB, 06/2015: t-MDS with multilineage dysplasia.
BMB, 01/2016: t-AML (50% myeloid blasts).
Immunophenotype: The atypical large cells in both BMBs show a classic Reed-Sternberg cell immunophenotype: CD30+/CD20-/CD25+/PAX5 weak/CD15-/EBER-. T cells show predominance of CD4 cells over CD8 cells.
Cytogenetics: 12/2012: karyotype failed. No evidence of FIP1L1-PDGFRA fusion.
06/2015 (therapy-related MDS): Complex karyotype, including monosomy 5.
Molecular studies: 06/2015 (t-MDS): (RapidHeme NGS panel, 94 genes) on marrow aspirate: TP53 p.G245D mutation (VAF: 87.9%).
Proposed diagnosis: Bone marrow involvement by classical Hodgkin lymphoma.
Interesting feature(s) of submitted case: Identifying CHL presenting primarily in the bone marrow can be challenging. Tumor cells are often rare and masked by distortion of the surrounding marrow with fibrosis and a reactive infiltrate. In this case, the long history of RA and MTX therapy represented additional confounding factors, especially in the first BMB, and an autoimmune process was initially favored. The possibility of a Hodgkin-like lesion secondary to MTX-induced immunosuppression was considered in the second BMB, but the typical immunophenotype and the absence of EBV favored CHL; also, MTX cessation did not result in clinical improvement. This case stresses the importance of considering the possibility of CHL in a cytopenic patient with marrow fibrosis, particularly when marrow eosinophils are increased.

EAHP18-BMWS-221

BRAF mutant classical Hodgkin lymphoma in the bone marrow of a patient with clinically suspected drug-related eosinophilia with systemic symptoms and history of Langerhans cell histiocytosis

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Case description: A bone marrow biopsy of a 46 years old woman was taken due to an unexplained pancytopenia along with a clinically suspected drug-related eosinophilia with systemic symptoms because of a sinusitis treated with amoxicillin/clavulanate. The biopsy showed subtotal infiltration by classical Hodgkin lymphoma (HL, submitted specimen). Upon histopathological diagnosis, radiology revealed a wide-spread disease infiltrating all lymph nodes of the trunk, the spleen and the skeleton. BEACOPP polychemotherapy was applied achieving complete remission. Control PET/CT one year later discovered a positive lytic lesion in the os ilium suspect of recurrent HL. Lesional biopsy revealed Langerhans cell (LC) proliferation (no submitted, see accompanying PPT). Complement of the anamnesis uncovered a surprising fact: at the age of 6 years, the patient had suffered from Langerhans cell histiocytosis (LCH) of the temporal bone that was treated by surgical curetting. The questions were: Was this proliferation of LC in the os ilium reactive or manifestation of a "true" LCH? Were both the HL and the LCH related?
To answer these questions, the Cancer Hotspot assay was employed (ThermoFisher). LC (N=250) and Hodgkin and Reed-Sternberg cells (HRSC, N=860), identified by their CD1a and CD30 positivity, respectively, were laser-capture-microdissected from immunohistochemically stained uncoverslipped slides, DNA was extracted and preamplified. $BRAF^{V600E}$ was detected in the LC, yet the assay failed in HRSC. Therefore the Idylla ctBRAF technology was applied (Biocartis). Analysis of the DNA extracted from the microdissected HRSC showed a $BRAF^{V600}$ mutation too.
Biopsy fixation details: buffered formalin
Frozen tissue available: no
Details of microscopic findings: Bone marrow biopsy with diffuse infiltrates of HL
Immunophenotype: positive: CD30, CD15dim, PAX5
negative: ALK, CD1a, Langerin, EBER
Cytogenetics: not done
Molecular studies: Idylla ctBRAF: $BRAF^{V600}$+
Proposed diagnosis: Bone marrow infiltration by classical HL
Interesting feature(s) of submitted case: The most prevalent lymphoma associated with LCH is HL (0.3% rate). The lymphoma/LCH relationship has not been fully understood. Pina-Oviedo et al. did not detect BRAF and MAP2K1 mutations in six cases of concomitant diseases (Mod Pathol 2017;30:734) and concluded that such LCH might be benign processes; it has been suggested to call them "LC-like" lesions (Hum Pathol 2006;37:32). There are different possible scenarios for this concurrence: HL induces LCH, HL therapy causes LCH, LCH is an immune response to HL, and LCH and HL share the same etiology. Our case substantiates the last hypothesis since $BRAF^{V600}$ mutations were detectable in both patient's neoplasms. While for the LCH this was expected, only one HL case bearing $BRAF^{V600E}$ has been reported yet (Haematologica 2017;102(s2):85). Regarding the rarity of this mutation in HL, it is tempting to assume a clonal relationship between both neoplasms. However, as LCH originate from myeloid precursors and HL from B-cells, only a common $BRAF^{V600E}$+ haematopoietic stem cell would be a potential mechanistic explanation. Indeed, a case of concurrent hairy cell leukemia and LCH sharing $BRAF^{V600E}$ has been described. Finally, our case underscores the importance of histological examination of equivocal PET+ lesions after lymphoma therapy since e.g. LCH in this context can imitate recurrence.
This case has been published: Ann Hematol 2018;97:355

EAHP18-BMWS-302

Classical Hodgkin lymphoma and plasma cell myeloma: a mixed marriage in the marrow

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Case description: A 68-year-old male with history of pulmonary sarcoidosis presented with fever, leukopenia (WBC 1.8 x 10^9/L) and anemia (HGB 7.5 g/dL). Serologic studies demonstrated an elevated free lambda light chain (134.5mg/L) with a lambda:kappa ratio of 9.2. PET scan demonstrated focal FDG avidity in multiple vertebrae. A bone marrow biopsy was performed.
Biopsy fixation details: Formalin-fixed, paraffin embedded. Decalcified core biopsy.
Frozen tissue available: Unavailable
Details of microscopic findings: The core biopsy shows a hypercellular marrow (70%) for age. The biopsy is involved by an atypical infiltrate (involving 20-30% of the marrow) that contains scattered large, atypical mononuclear cells with prominent single nucleoli and moderately abundant cytoplasm admixed with numerous histiocytes and small lymphocytes as well as occasional plasma cells and eosinophils. Rare binucleated Reed-Sternberg cells are also present. The aspirate smear showed small and occasional atypical plasma cells (15% of cellularity).
Immunophenotype: The large atypical cells in the areas of infiltration are CD30+ EBER1+ PAX5(weak)+ CD20(subset weak)+. In addition, there are ~10-15% lambda restricted CD138+ plasma cells present in small, interstitial clusters both within and between the areas involved by the infiltrate.
Cytogenetics: 46,XY[20]
Molecular studies: 68 Gene Hematologic Malignancy NGS panel is negative for disease associated mutations. CD138 enriched myeloma FISH panel negative for t(4;14), t(11;14), t(14;16), deletion TP53/monosomy 17, and deletion of 1p36/gain of 1q21.
Proposed diagnosis: Classical Hodgkin lymphoma (CHL) with concomitant plasma cell myeloma (PCM)
Interesting feature(s) of submitted case: 1. The serologic and radiologic findings led to a pre-biopsy consideration of PCM. While PCM was indeed evident, the presence of CHL was unexpected. Of note, the FDG avid bony lesions may have been unrelated to the PCM, as they disappeared after CHL directed chemotherapy (which might also have had activity against the PCM).
2. Bone marrow involvement in CHL is rare (5% of cases) and marrow involvement as its primary presentation even more so. As the marrow lacks lymphatics, its involvement by CHL indicates vascular dissemination and stage IV disease.
3. Coexistent CHL and PCM in the marrow is even less common.
4. Since polyclonal bone marrow plasmacytosis often accompanies CHL, in the absence of any serologic and radiologic clues, the clonal nature of these cells could have been overlooked and the diagnosis of a second neoplasm missed.

EAHP18-BMWS-325

Primary bone marrow presentation of classical Hodgkin lymphoma with coexistent myelodysplastic syndrome.

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Case description: A 52-year-old man with a remote history of diffuse large B-cell lymphoma in 1998 that was initially treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (RCHOP). Relapse in 2003 was treated with ifosfamide, carboplatin and etoposide (ICE), and autologous stem cell transplant. He presents now (2017) with fatigue. No lymphadenopathy noted. CBC shows WBC 0.95 x 109/L, RBC 2.75 x 1012/L, and PLT 54 x 109/L. This new pancytopenia prompted a bone marrow biopsy.
Biopsy fixation details: Formalin
Frozen tissue available: No.
Details of microscopic findings: H&E stained sections of the bone marrow biopsy shows normocellular bone marrow (~50%) with two sizable polymorphic aggregates that involve ~10% of bone marrow. These aggregates contain an admixture of small mature lymphocytes, macrophages and eosinophils, with scattered large atypical cells that are both mono- and bi-lobated, with prominent eosinophilic inclusion-like nucleoli, and moderate amounts of clear cytoplasm, resembling Hodgkin and Reed-Sternberg cells.
In addition, megakaryocytes show cytologic atypia (hypolobated and hyperchromatic forms, micromegakaryocytes, focal clustering) in >10% of cells, and the Giemsa-stained aspirate smear shows dysplastic erythroid precursors (nuclear budding, irregular nuclear contours) in >10% of cells.
Immunophenotype: Immunohistochemical stains performed on the biopsy core show that the large atypical cells within the aggregates are positive for CD30, PAX5 (dim), MUM1 and EBER1 (by in situ hybridization) with a subset expressing CD15; they are negative for CD20, CD45, CD79a, BCL6, BOB1 and OCT2. CD34 highlights rare blasts (<5%). CD3 highlights numerous T-cells within aggregates with a subset expressing PD1. CD61+ highlights the increased number of abnormal megakaryocytes.
Cytogenetics: Cytogenetic studies show an abnormal male karyotype:
46,XY,+1,der(1;7)(q10;p10)[3]/46,XY[17].
FISH studies are positive for deletion 7q (present in 5.7% nuclei, normal <4.4%) and negative for del 5q, monosomy 5, monosomy 7, trisomy 8, and deletion 20q.
Molecular studies: Not provided.
Proposed diagnosis: 1) Classical Hodgkin lymphoma; and
2) Myelodysplastic syndrome with multilineage dysplasia (MDS-MLD)
Interesting feature(s) of submitted case: 1) Primary Hodgkin lymphoma of the bone marrow is rare in HIV-negative patients
2) Simultaneous presence of primary Hodgkin lymphoma and myelodysplastic syndrome is extremely rare with only a few cases reported in the literature
3) While the MDS is likely to be a therapy-related myeloid neoplasm, it is possible that the Hodgkin lymphoma may also be related to the immunosuppressive effects of prior therapy

EAHP18-BMWS-418

Classic Hodgkin lymphoma with co-existent monoclonal B-cell lymphocytosis (MBL).

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Case description: An 89 year-old female patient presented with 2 months history of fevers and weight loss. CT revealed low volume lymphadenopathy with no mass lesions or further abnormality/suspected primary malignancy. Laboratory findings included an IgM paraprotein (7g/L), Haemoglobin concentration of 114 g/L, WBC of 5.2 x10*9/L and a platelet count of 134 x10*9/L. Bone marrow sampling was performed to assess for any evidence of an underlying low grade lymphoma, particularly lymphoplasmacytic lymphoma.
Biopsy fixation details: 10% neutral buffered formalin, EDTA decalcification
Frozen tissue available: None available
Details of microscopic findings: : The sample is a very short and fragmented and shows evidence of a hypercellular (75%) bone marrow. In two areas, there are a handful of scattered large lymphoid cells with irregular / multilobated nuclei with nucleoli. These cells show the morphological features of Hodgkin Reed-Sternberg (HRS) cells. In the background, there are numerous histiocytes, small T cells and small B-cells (the latter ~15%) in addition to plasma cells and eosinophils. Here, WHO grade 2, Bain 3 fibrosis is noted. There is background of maturing trilineage haematopoiesis.
Immunophenotype: Immunohistochemistry: The large HRS cells show the following phenotype: CD30+, CD15+ (very weak), CD20-, CD79a-, PAX5+ (weak), MUM1+, BCL6+ (weak), EBER- (ISH), CD45-, CD3-, ALK-, CD3-. Immunocytochemistry/flow cytometry: the large cell population seen in the marrow is not detected in the peripheral blood sample examined. However, the small B-cell population (0.5 x 10^9/L) is present and shows expression of CD5, CD19, weak CD20, moderate CD22, minimal CD23 (6%), CD43, weak CD81, weak CD200 and kappa light chains. There is no expression of CD38.
Cytogenetics: No evidence of CLL (i.e. deletions of chromosomes 11q (ATM), 13q and 17p (TP53), and trisomy of chromosome 12) or mantle cell lymphoma [IGH-CCND1 t(11;14)] related molecular alterations.
Molecular studies: Not performed as patient passed away 3 days after diagnosis.
Proposed diagnosis: Classic Hodgkin lymphoma with co-existing CLL-like MBL.
Interesting feature(s) of submitted case: The UK prevalence of CLL-like MBL in the >60 year old population is ~5%. Some studies suggest that a percentage of diffuse large B-cell lymphomas can present with clonally associated MBL. However, we are not aware of any publications/case reports of classic Hodgkin lymphoma presenting with associated MBL.

EAHP18-BMWS-483

Hodgkin Lymphoma; primary presentation in the bone marrow?

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Case description: In 2013 a 29 year old man presented with fever, fatigue, low back pain and complaints of itching without skin lesions. On physical examination a sick, tired man without lymphadenopathy was seen. Lab results showed a Hb of 8,4 mmol/l, WBC 11,2 x 109/l, normal platelets but a LDH of 800U/l. HIV and EBV serology was negative. On PET CT scan a diffuse skeletal FDG uptake and a few lymphnodes in the anterior mediastinum, were seen. A bone marrow biopsy was performed, the aspirate revealed a dry tap. During mediastinoscopy a biopsy on a regional lymphnode was performed. While waiting for the definitive pathology results the general condition of the patient declined. He developed a serious fever with negative blood cultures, the LDH level increased significantly.
Biopsy fixation details: 4% buffered formalin
Frozen tissue available: no
Details of microscopic findings: Bone marrow: the marrow is completely replaced by sheets of large irregular blasts with focal signs of infarction. The blasts show large irregular polymorphic nuclei and eosinophilic cytoplasm. The blasts strongly stained for CD30, CD15 and weak for PAX-5. The B cell markers CD20 and CD79a were negative as were the T/NK markers CD2, CD3, CD7, Granzym B, CD56. The myeloid markers MPO, lysozyme, CD68 and CD117 stained negative. EBER and ALK-1 were also negative. The mediastinal lymphnode: the morphology of the lymphnode was rather poor, but in some parts of the lymphnode comparable with the bone marrow. The lymphnode showed sheets of the same blast with the same immune phenotype. No typical Reed Sternberg blast were seen and the classic Hodgkin background of small B cell, eosinophils and fibrosis lacked. Surprisingly, the MIB-1 staining showed a very high proliferation fraction, nearly every blast was in cyclus.
Immunophenotype: The blasts strongly stained for CD30, CD15 and weak for PAX-5. The B cell markers CD20 and CD79a were negative as were the T/NK markers CD2, CD3, CD7, Granzym B, CD56. The myeloid markers MPO, lysozyme, CD68 and CD117 stained negative. EBER and ALK-1 were also negative.
Cytogenetics: not available
Molecular studies: not available
Proposed diagnosis: aggressive lymphoma, unclassifiable
Interesting feature(s) of submitted case: : This case represents a malignant lymphoma that presents with extensive generalized bone marrow infiltration in absence of lymphadenopathy. Morphology and immunophenotype are consistent with classical Hodgkin lymphoma. Only upon detailed re-examination, a few small lymphnodes in the mediastinum were noted and this presentation is highly unusual. The patient was treated as a Hodgkin stage IVB disease with BEACOPPesc. After 6 cycles, the general condition of the patient improved and the lesions on the PET-CT scan disappeared complete. At last follow up of 50 months after completion of treatment, the patient still is in complete remission.
The clinical presentation with almost exclusive bone marrow involvement is highly unusual or classical Hodgkin lymphoma and alternative interpretations were considered. However no arguments for other classifications, including lymphoid proliferations with secondary Hodgkin-type blasts were supported. Alternatively, classification of aggressive lymphoma unclassifiable may be chosen, based on the atypical clinical presentation, the lack of a typical Hodgkin background together with the high proliferation index.
this is an example of the dilemma of lymphomas with a Hodgkin-like phenotype but which does not fit into the classical Hodgkin basket because of their clinical presentation or morphology.

EAHP18-BMWS-486

Classical Hodgkin lymphoma presenting as pancytopenia and massive bone marrow involvement.

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Case description: A 76-year-old HIV-negative female patient carrying a diagnosis of T-cell large granular lymphocytic leukemia (T-LGL) for ten years, without treatment, was admitted to our hospital in 10/2017 for pancytopenia with fever, diarrhea and fatigue in the preceding months. She was initially treated with antibiotics and G-CSF but readmitted six weeks later for a subdural hematoma due to a fall. A CT scan showed marked splenomegaly (16cm) and slightly enlarged (2-11mm) mediastinal, peri-aortic and iliac lymph nodes. Due to persistent pancytopenia (WBC: 4.8 G/l, Hb: 76 g/l, PLT: 75 G/l) a bone marrow aspiration and biopsy were performed. PET-CT showed diffuse bone marrow involvement of the axial and appendicular skeleton, splenic infiltration and hypermetabolic mediastinal, retroperitoneal and iliac lymph nodes, with SUVmax ranging from 2.8-9.1 g/ml. The patient refused treatment and was transferred to palliative care, where she expired 5 days later.
Biopsy fixation details: F.A.Z (formalin, acetic acid and zinc salt).
Frozen tissue available: No.
Details of microscopic findings: The bone marrow spaces were 90% cellular and predominantly involved by a polymorphic, multifocal and diffuse infiltrate consisting of histiocytes and small lymphocytes, among which were interspersed large atypical cells suggestive of Hodgkin/Reed Sternberg (HRS) cells. There were essentially no eosinophils. A less prominent interstitial lymphocytosis consisting of small lymphocytes with dense chromatin was also present. Residual trilinear hematopoietic tissue was unremarkable, with grade I reticulin fibrosis, while a more dense reticulin network was seen in the tumoral areas. There was no sign of hemophagocytosis. The aspirate showed several large lymphoid cells suggestive of Reed-Sternberg cells.
Immunophenotype: The HRS cells were positive for CD30, CD15, MUM1 and showed weak expression of PAX5; they were negative for CD45, ALK, CD3, CD5 and CD20. The accompanying infiltrate of small lymphocytes consisted of CD4+ T cells negative for PD1 and CXCL13. The interstitial lymphocytosis was predominantly composed of CD8+ TIA1+ CD57+/- cells. In situ hybridization for EBV was negative.
Cytogenetics: Not performed.
Molecular studies: Multiplex PCR (Biomed-2) showed monoclonal rearrangement of IGH, IGK, TRB and TRG genes.
Proposed diagnosis: Concomitant bone marrow infiltration by EBV-negative classical Hodgkin lymphoma, and T-LGL leukemia.
Interesting feature(s) of submitted case: This is an unusual presentation of an EBV-negative classical Hodgkin lymphoma (HL), with pancytopenia due to diffuse bone marrow infiltration and hepatosplenomegaly, without conspicuous lymph node involvement. Few primary bone marrow classical HL have been reported in HIV-negative patients (Morita Y. Intern Med. 2015;54:1393). The clinical course is almost invariably aggressive. This case was interesting because of the well preserved morphology and the numerous typical HRS cells in the biopsy as well as the aspirate.
Furthermore, while the association of a HL and a T-LGL leukemia has been previously recognized (Lamy T. Blood. 2017;129:1082), this case is remarkable by the coexistence of both neoplasms in the bone marrow. Accordingly, the molecular studies demonstrated concomitant IGH and TCR rearrangements that were ascribed to the HRS and T-LGL, respectively.

EAHP18-BMWS-511

Primary bone marrow classical Hodgkin Lymphoma

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Case description: A 49-year-old male patient was admitted to the Hematology Unit of Attikon University Hospital on February 2011 due to a 2-month history of fever of undetermined origin and night sweats. He reported daily afternoon fever of up to 39 °C. Clinical examination was unremarkable. A complete blood count showed Hb 9.7 g/dL, WBC 9.21 x10^9/L (neutrophils 66%, lymphocytes 28%, monocytes 5%, eosinophils 1%) and PLT 380 x10^9/L. Erythrocyte sedimentation rate was 130 mm (first hour) and C-reactive protein (CRP) was 128mg/L (normal range: 0.00-6.00 mg/L). Tests of overt hemolysis were negative. Coagulation, electrolytes, liver, renal, thyroid function tests, autoimmune screens, hepatitis screening and tumor markers were within normal range. LDH was slightly elevated: 465 U/L. A whole body CT scan did not reveal abnormal findings. A bone marrow (BM) biopsy was performed on mid January 2011 which revealed findings suspicious for classical Hodgkin lymphoma (HL). A second BM biopsy was performed one month later **(submitted slides)** with similar histologic findings. The patient received 8 cycles of ABVD for primary BM cHL and achieved complete response by conventional re-staging with CT, PET-CT and BM biopsy (late November 2011, **illustrations in attached pdf**). Five years later, the patient readmitted with B symptoms and CT showed a single right mediastinal lymph node with short axis of 1.5cm and a single right hilar lymph node with short axis of 1.4 cm (SUVmax of 2.7 and 2.4 in PET-CT scan, respectively). Additionally, PET-CT scan revealed low-grade 18-FDG uptake (SUVmax 2.0 and 3.6) in left axillary lymph nodes and diffusely increased uptake in the bone marrow. BM biopsy (late November 2016) confirmed relapse of the disease (**illustrations in attached pdf**). Two months later the patient died from cardiac arrest without receiving any further treatment.
Biopsy fixation details: AZF (fixation)/Decal (decalcification)
Frozen tissue available: No.
Details of microscopic findings: Histologically, the bone marrow was hypercellular with predominance of myeloid elements. Of interest was the focal presence of discrete, well demarcated fibrotic areas (~30% of the total BM area), containing a polymorphic inflammatory infiltrate and a small number of scattered large atypical cells. Typical Reed-Sternberg cells were not found.
Immunophenotype: The polymorphic inflammatory infiltrate consists of small CD3+ T cells [CD4>CD8], small CD20+ B cells, CD138+ plasma cells, CD68+ histiocytes, MPO+ granulocytes and eosinophils. The large atypical cells were CD30+.
Cytogenetics: Not performed.
Molecular studies: Not performed.
Proposed diagnosis: Primary BM classical Hodgkin Lymphoma
Interesting feature(s) of submitted case: Bone marrow involvement is present at the time of diagnosis in 5% to 15% of cases of cHL (stage IV). Primary BM cHL is very rare (0.25%) and occurs most often in HIV+ patients. An interesting feature of this case is that the patient was HIV-. Furthermore, he benefited a complete long lasting response to ABVD chemotherapy a feature that further supports the diagnosis of primary BM cHL which on the histological level was established with caution as suspicious for cHL.

EAHP18-BMWS-513

Primary Bone Marrow Presentation of Classical Hodgkin Lymphoma

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Case description: A 29 year old woman consulted to internal medicine in December 2015 after six month-history of asthenia, recurrent fever, chills and night sweats.
Physical examination was normal showing no enlarged lymph nodes or hepatosplenomegaly. CT scan did not find enlarged lymph nodes or masses.
The laboratory tests showed Hb 116 g/L, Platelets 314x109/L, WBC 5.27x109/L (lymphocytes 1.3x109/L). LDH 563 U/L (N=250-450). Epstein-Barr Virus positive (18.456 c/ml copies). HIV negative.
Bone marrow biopsy was performed. In the light of the results, a PET-CT scan was carried out showing FGD (Fluordesoxiglocose-F18) hypercaptation in small lymph nodes in cervical region, axillary (SUV 18), mediastine (SUV 10), retroperitoneal and inguinal (SUV 23), diffuse hypercaptation of spleen, multiple focal lesions in liver (SUV 17) as well as bone marrow diffuse FDG hypercaptation with multiple focal lesions.
The patient received chemotherapy (4 cycles ABVD and 8 cycles of AVD due to bleomycin toxicity). She had a complete remission confirmed by no disease activity in repeat bone marrow biopsy and PET–CT scan.
Biopsy fixation details: B16-5058 fixation with Bouin's solution, decalcification with Decalcifier II Surgipath. B16-05059 fixation with formalin 10%, decalcification with formic acid 10%
Frozen tissue available: No
Details of microscopic findings: The bone marrow biopsy was hypercellular with a complete loss of adipose tissue. It presented fibrous areas with infiltration by atypical large cells with Hodgkin or Reed-Sternberg morphology, accompanied with mature lymphocytes, neutrophils and eosinophils.
Hematopoietic cells did not show any alteration.
Immunophenotype: The atypical cells were CD30+, CD15+, PAX5 weak+, CD20-, EBER+, LMP-1 -
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: Hodgkin lymphoma presenting as primary bone marrow classical vs predominantly bone marrow infiltration by systemic classical Hodgkin lymphoma.
Interesting feature(s) of submitted case: The clinical picture of a primary bone marrow presentation classical Hodgkin lymphoma is uncommon and primarily described in HIV-positive patients. The presence of hypercaptant lymph nodes by PET in both sides of diaphragm indicates that most probably it is a conventional classical Hodgkin lymphoma clinically presenting in the bone marrow.The small size of the lymph nodes, not palpable and not identified by the CT scan (and not biopsied) may suggest that it is a primary bone marrow lymphoma. A PET scan should be recommended in these cases.

EAHP18-BMWS-540

Bone marrow presentation of classic Hodgkin lymphoma in a patient with rheumatoid arthritis

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Case description: This is a 59 yo male who had history of rheumatoid arthritis since 2015. He had been treated with Etanercept and methotrexate. He presented with normocytic anemia and mild leukopenia in early 2017. Initially, it was thought that the cytopenia was caused by the medication. However, his cytopenia persisted after cessation of treatment. In addition, patient also showed fever, chills and intermittent night sweats. Physical examination and chest imaging studies failed to reveal any significant lymphadenopathy at the time of visit. Clinically, an infectious vs lymphoproliferative etiology was suspected. A bone marrow evaluation was performed in May 2017.
Biopsy fixation details: Bone marrow biopsy was fixed in the 10% buffered formalin after brief decalcification and embedded in paraffin.
Frozen tissue available: Not applicable
Details of microscopic findings: Bone marrow biopsy showed a hypercellular marrow with maturing trilineage hematopoiesis. However, a large portion of bone marrow space was replaced by fibrosis and mixed infiltrates including small lymphocytes, histiocytes, eosinophils, and plasma cells admixed with scattered large atypical lymphoid cells. These large atypical cells were predominantly mononuclear and few multinucleated forms. Some of them contained distinct nucleoli and ample cytoplasm. Bone marrow aspirate smear showed maturing trilineage hematopoiesis and very few atypical lymphoid cells with large irregular nucleus and basophilic cytoplasm. These atypical cells were morphologically suspicious for R-S cells or variant Hodgkin cells.
Immunophenotype: Reticulin stain showed focally increased fibrosis in involved marrow. A panel of immunohistochemical stains was performed on marrow biopsy including CD3, CD20, PAX-5, CD30, CD15, CD45, and EBER in situ hybridization. These large atypical cells were positive for CD30, CD15 (focal), PAX5 and EBER; negative for CD20, CD3 and CD45. CD3 stains background small T cells.
Cytogenetics: Normal male karyotype, 46,XY[20]
Molecular studies: Not applicable
Proposed diagnosis: Classic Hodgkin Lymphoma
Interesting feature(s) of submitted case: Bone marrow involvement in classic Hodgkin lymphoma is not common, largely representing extranodal involvement of an advanced disease (Stage 3 or 4). Based on our limited observation, some of these cases occurred in patients with compromised immune system due to various reasons, including HIV infection, iatrogenic immunosuppression and immune senescence. For the current case, it is postulated that the disease is likely associated with compromised immune response due to Etanercept and methotrexate treatment.
Follow-up clinical study: CT scan after bone marrow evaluation showed splenomegaly and retroperitoneal lymphadenopathy. Patient was treated with 6 courses of ABVD and currently in remission.

BONE MARROW WORKSHOP SESSION 3

Aggressive B-NHL

Chairs: F. Fend, A. Zamo

EAHP18-BMWS-255

De novo CD5 positive diffuse large B-cell lymphoma of the bone marrow.

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Case description: The patient is a 64 year old male with seropositive rheumatoid arthritis presenting with fatigue, shortness of breath, fevers to 101F, night sweats and pancytopenia. Physical examination is notable for splenomegaly. Labs are notable for mildly elevated liver function tests, elevated ferritin (4039 ng/dl), LDH (2241 IU/L) and triglycerides (264 mg/dL). The patient was admitted for further work-up including bone marrow biopsy.
Peripheral blood smear revealed a cold agglutin disease with presence of atypical large lymphoid cells. Bone marrow biopsy revealed a de novo CD5positive diffuse large B-cell lymphoma (DLBCL).
In addition, 5 out of 8 criteria for hemophagocytic lymphohistiocytosis (HLH) were present (fevers, splenomegaly, cytopenia, hypertriglyceridemia, and serum ferritin > 500ug/L). HLH was thought to be secondary to the DLBCL.
He was treated with 6 cycles of dose adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin hydrochloride (DA R-EPOCH) and 4 cycles of high dose intrathecal methotrexate (MTX). Bone marrow biopsy after 4 cycles of DA R-EPOCH demonstrated complete response (CR) (approximately 15 months).
Biopsy fixation details: Bouin's fixative
Frozen tissue available: N/A
Details of microscopic findings: Peripheral blood smear revealed a cold agglutin disease. Few atypical large lympoid cells were seen in the peripheral blood with pleomorphic nuclei and hyperchromasia. The bone marrow biopsy was a dry tap. Touch preparation showed similar atypical large lymphoid cells, some in clusters. Bone marrow biopsy revealed a large atypical lymphoid infiltrate, with both nodular and sinusoidal patterns. The large lymphoid cells were highly pleomorphic with vesicular chromatin and multiple prominent small nucleoli.
Immunophenotype: Flow cytometry detected a kappa monotypic B-cell population in the monocyte gate, coexpressing CD5 (dim), CD10, CD22, FMC7 and not expressing CD23. Immunostains confirmed the flow cytometry phenotype, CD5+, CD10+ and CD20+. Ki-67 (proliferation index) was high, 80-90%. EBV by EBER in situ hybridization method was negative. BCL1 and SOX11 were negative.
Cytogenetics: No analyzable metaphases were observed during chromosome analysis. FISH for MYC, BCL2 and BCL6 were all positive ("triple hit").
Molecular studies: N/A
Proposed diagnosis: De novo CD5+ diffuse large B-cell lymphoma, "triple hit", germinal center type.
Interesting feature(s) of submitted case: The differential diagnosis of a large CD5+ large B-cell lymphoma includes de novo diffuse large B-cell lymphoma (DLBCL), pleomorphic mantle cell lymphoma (MCL), Richter's transformation of chronic lymphocytic leukemia (CLL) and paraimmunoblastic variant of CLL. CD23 was negative by flow cytometry, and no small or intermediate lymphoid population was identified, thus CLL-associated disease is unlikely. BCL1 and SOX11 were negative providing no support for MCL. De novo CD5+ DLBCL was favored, which is associated with 1) worse prognosis; 2) prone to central nervous system recurrence; and 3) associated with intravascular large B-cell lymphoma. Random skin biopsies were performed and no evidence of intravascular lymphoma was detected.

EAHP18-BMWS-279

Primary bone marrow presentation of a high-grade B-cell lymphoma with MYC and BCL2 rearrangements and blastoid features

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Case description:
A 46-year-old man with no past medical history presented with complaints of night sweats, fatigue of 2 weeks' duration. A complete blood count showed anemia and thrombocytopenia
WBC = 6 x 10E9/L (Neut 2.05 x 10E9/L, Lymph 1.92 x 10E9/L, Blasts/Abnormal lymphs 0.56 x 10E9/L), Hb = 9 g/dL, Plt = 12 x 10E9/L.
Peripheral smear showed atypical mononuclear cells with open chromatin, nucleoli, basophilic cytoplasm.
He had small neck nodes, 1-1.5 cm. No other lymphadenopathy or splenomegaly was noted. A bone marrow biopsy was performed and was a dry tap.
Meanwhile, a PET/CT was performed and showed high uptake in numerous small cervical, axillary, retroperitoneal lymph nodes and extensive osseous uptake. A cervical lymph node biopsy was performed.
Biopsy fixation details: Formalin-fixed.
Frozen tissue available: No.
Details of microscopic findings:
The bone marrow is replaced by atypical mononuclear cells with high N/C ratio, irregular nuclei, fine chromatin, small nucleoli and minimal cytoplasm (blastoid).
The lymph node architecture is effaced by sheets of atypical large lymphoid cells with pleomorphic nuclei, vesicular chromatin, prominent macronucleoli, and abundant amphophilic cytoplasm. Blastoid cells are not identified.
Immunophenotype: Bone marrow immunohistochemistry and flow cytometry: Positive: PAX-5, BCL2, CD10, CD19, CD20 (dim), CD79a, CD38, HLA-DR Negative: CD34, CD3, TdT, MPO, sIg, CD4, CD56, CD14, CD64 Lymph node immunohistochemistry: Positive: CD20 (strong), PAX-5, CD10, BCL6, BCL2 (80%), C-MYC (40-50%) Negative: MUM1, CD5, BCL1, TdT, EBER-ISH
Cytogenetics: Peripheral blood Karyotype 47-49,X,Y,+1,del(1)(p12),del(5)(q31q34),t(8;14)(q24.2;q32), del(10)(q23),der(18)t(14;18)(q32;q21.3),+1-4mar,inc[cp3] /46,XY[16]. FISH POSITIVE: IGH/BCL2 and MYC/IGH fusions. Negative: BCL6 rearrangement. Lymph node Karyotype 48,XY,del(5)(q31q34),+8,add(9)(p22),dup(12)(q13q22), t(14;18)(q32;q21),+17[19]/46,XY[1]. FISH POSITIVE: Gain of MYC signal. Negative: MYC and BCL6 rearrangements. Shared cytogenetic aberrations between lymph node and peripheral blood : del(5)(q31q34) and t(14;18)
Molecular studies: NGS mutational analysis of 479 cancer genes Lymph node: CDKN2A, CDKN2B deep deletion, PTEN deep deletion, CNOT3 p.R57Q, CREBBP p.W1502L, DDX3X p.L353V, EBF1 c.134+5G>T, MAP2K1 p.F53C, SIN3A c.1161+1G>C Peripheral blood: MYC structural variant, CCND3 p.I290R, CNOT3 p.R57Q, CREBBP p.W1502L, EBF1 p.Y75*, MAP2K1 p.F53C, SIN3A c.1161+1G>C Shared genomic aberrations between lymph node and peripheral blood: CNOT3 p.R57Q, CREBBP p.W1502L, MAP2K1 p.F53C, SIN3A c.1161+1G>C
Proposed diagnosis: High-grade B-cell lymphoma with MYC and BCL2 rearrangements (Bone Marrow) with concurrent asymtopmatic diffuse large B-cell lymphoma (Lymph node)
Interesting feature(s) of submitted case:
This is a unique case of a synchronous symptomatic extranodal high-grade B-cell lymphoma (HGBCL) with MYC and BCL2 rearrangements and asymptomatic nodal diffuse large B-cell lymphoma (DLBCL).
The absence of a prior or concurrent low grade B-cell lymphoma and evidence of some shared genomic aberrations suggest either transformation of DLBCL to HGBCL or divergent evolution from a common progenitor cell.
This high-grade B-cell lymphoma also shows some features of immaturity (morphology, dim CD45, weak/absent CD20, absent sIg) raising a differential diagnosis of B-lymphoblastic leukemia/lymphoma (B-ALL/LBL).
It is accepted that cases with an immature B-cell phenotype and TdT expression should be classified as (B-ALL/LBL) (WHO 2016). However, the extent and intensity of TdT expression and minimum criteria required to distinguish HGBCL with blastoid features from B-ALL/LBL remain a matter of debate.

EAHP18-BMWS-296

Primary bone marrow high grade B cell lymphoma with MYC and Bcl6 gene rearrangement

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Case description: A 62 year old lady with known multiple sclerosis presented to the emergency department with sepsis and was found to be pancytopenic (HB-84g/l, WCC-0.8, neutrophils- 0.6, platelets 14, LDH-6000). Subsequent bone marrow aspirate showed 20% infiltration by lymphoid blasts ?ALL/other high grade non Hodgkin lymphoma. Flow cytometry performed on peripheral blood showed the lymphoid blasts to express CD19, CD20, CD79a, CD38 and CD10 but were negative for TDT, and all the T cell antigens. The bone marrow trephine biopsy showed dense interstitial and paratrabecular infiltration by monomorphic medium sized lymphoid blasts with conspicuous intermixed tingible body macrophages, reminiscent of 'Burkitts' lymphoma.
CT and PET scans showed no evidence of disease elsewhere.The patient was is currently on the 5th cycle of R-CHOP as she was deemed an unsuitable candidate for CODOX-M-IVAC
Biopsy fixation details: 24 hours fixation with 10% buffered formalin
Frozen tissue available: No
Details of microscopic findings: The bone marrow trephine showed dense interstitial and paratrabecular infiltration by sheets of monomorphic medium sized lymphid blasts with conspicuous interspersed tingible body macrophages, imparting a 'Starry sky' appearance to the biopsy.
Immunophenotype: CD20+, CD79a+, CD10+, BCL6+, C-MYC +(80% at least), BCL2-, TDT-, CD3-, CD5-, CD23-, CYCLIN D1-
Cytogenetics: not done
Molecular studies: FISH performed on peripheral blood - MYC and bcl6 genes rearranged. BCL2 not rearranged
Proposed diagnosis: Primary bone marrow high grade B cell lymphoma with MYC and BCL6 gene rearrangements
Interesting feature(s) of submitted case: This is primary bone marrow infiltration by high grade B cell lymphoma with MYC and BCL6 gene rearrangements, with to date no evidence of disease elsewhere as seen with repeat CT scans. She is currently responding well to R-CHOP on the 5th cycle.

EAHP18-BMWS-300

Diffuse large B-cell lymphoma with massive involvement of the bone marrow and spleen

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Case description: Male patient born in 1952, with a previous history of spindle cell melanoma and basal cell carcinoma of the left leg in 2014 (treated by surgical resection - pT4a pN2c cM0), who presented in January 2017 with altered performance status, B symptoms, hypotension, mental confusion and altered liver tests (cholestasis). Blood analysis showed pancytopenia (leukocytes 4; hemoglobin 71; plaquettes 13) and increased LDH (671 UI, nl 135-225). A bone marrow (submitted) was performed, as well as a liver biopsy showing hepatocellular cholestasis, mild microvacuolar steatosis, and mild lymphohistiocytic portal infiltrate, without evidence of malignancy. A PET-CT demonstrated hypermetabolic splenomegaly, a focus of uptake in the liver, multiple bone hypermetabolic foci and several sus- and subdiaphragmatic lymph nodes. IPI was 5/5. The patient was treated by 2 cycles of R-CVP followed by 4 cycles of R-CHOP. Control PET-CT scans showed regression of the splenomegaly, and appearance of a pathological lymph node in the hilum of the spleen. At 3 months after the end of therapy liver hypermetabolism prompted a liver biopsy in September 2017 which showed infiltration by diffuse large B-cell lymphoma, CD20 negative. The patient then received salvage therapy with R-DHAP, under which PET-CT documented progressive disease, with appearance of additional lymphadenopathies. The patient was then switch to R-ICE, but disease progression continued. He is currently under gemcitabine-based chemotherapy plus Brentuximab.
Biopsy fixation details: FAZ.
Frozen tissue available: no.
Details of microscopic findings: Bone marrow biopsy: massive involvement of bone marrow spaces by sheets of large lymphoid cells, producing a diffuse interstitial pattern of infiltrate without significant intrasinusoidal component. The large lymphoid cells comprise an admixture of centroblastic and immunoblastic cells, sometimes with a histiocytoid appearance. There was no small cell component. The adjacent trilinear hematopoiesis showing mild dyserythropoiesis and atypical megacaryocytes.
Immunophenotype: Lymphoma cells are CD20+, PAX5+, CD3-, CD5-, BCL2+, BCL6+, CD30+, CD10-, MUM1-. Ki67 proliferation index evaluated to more than 80%. No monotypic light chain expression demonstrated.
Cytogenetics: Complex caryotype: 43~44,X,+X,-1,add(q42),-2,-4,add(6)(p22),add(6)(p23),del(7)(p12p22),-8,-9,add(13)(p11.2),add(14)(q32),add(15)(p11.2),-16,-17,-22,+5~6mar[cp2]/46,XY[18]
Molecular studies: FISH studies: BCL6 rearrangement; no BCL2 or MYC rearrangement.
EBER in situ hybridization: negative.
Proposed diagnosis: Diffuse large B-cell lymphoma NOS, CD5 negative, germinal center-like, according to Hans algorithm, with BCL6 gene rearrangement.
Interesting feature(s) of submitted case: Diffuse large B-cell lymphoma presenting in a patient with altered general status and pancytopenia, characterized by a disease distribution in the form of massive bone marrow involvement and splenomegaly, focal hepatic involvement, and lesser degree of lymphadenopathies. The disease featured an aggressive clinical course, resistance to standard therapy and to salvage therapy.
Futoshi Lioka et al. reported a unique subtype of DLBCL primarily involving the bone marrow, spleen and liver defined by FDG-PET combined with computed tomography (Leukemia & Lymphoma 2016; 57:2593,). In the 10 cases presented in that study, most patients had B symptoms poor performance status and hepatosplenomegaly as well as cytopenia and elevated LDH. In that series 5 of the 10 patients had a rearrangement involving BCL6, and all showed a non-germinal center B-cell immunophenotype.

EAHP18-BMWS-385

Burkitt lymphoma lacking MYC rearrangements and 11q aberrations in bone marrow

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Case description: 26-year-old HIV 1/2-negative woman presented with malaise, myalgia, and petechiae. CBC showed WBC 13.5 (4-11K/mcL), Hgb 11.5 (11.5-16 g/dL), Hct 32.8 (34-46%), MCV 77.7 (80-100 fL), Plts 31 (160-400 K/mcL) and she was started on dexamethasone for presumed idiopathic thrombocytopenic purpura (ITP). An abdomen/ pelvis CT showed a 3cm pelvic sidewall lobulated soft tissue mass and PET showed FDG-avid abdominal nodes, liver, and bone marrow. A bone marrow (BM) biopsy revealed extensive involvement by aggressive lymphoma. She was treated with chemotherapy with intrathecal prophylaxis and 5 months after diagnosis she has no evidence of disease on PET and follow up BM biopsies.
Biopsy fixation details: BM biopsies were 10% formalin-fixed, followed by routine processing after decalcification.
Frozen tissue available: NA
Details of microscopic findings: BM sections showed markedly hypercellular (100%) marrow completely replaced by a diffuse monotonous infiltrate composed of medium-size atypical lymphoid cells with round nuclei, finely clumped chromatin, small nucleoli, and scant cytoplasm with angulated retraction. Cytoplasmic vacuoles were seen on aspirate smears. A "starry sky" pattern was present with many mitotic figures and tingible body macrophages.
Immunophenotype: By immunohistology (IHC), the neoplastic cells expressed CD20, PAX5, BCL6, CD10, C-MYC, and weak MUM1, while negative for CD3, BCL2, TdT, CD23, and LMP1. EBER ISH was negative. The Ki67 index was 95%. Flow cytometry confirmed presence of abnormal mature B-cells positive for CD19, CD20, CD10, CD22(dim), CD38(br), CD45, and lambda light chain.
Cytogenetics: Conventional cytogenetics showed a normal female karyotype. FISH break-apart and IGH-MYC dual fusion probes (Abbott Molecular) showed no evidence of a MYC rearrangement. SNP-array analysis detected copy neutral loss of heterozygosity (CN LOH) of 1p and CN LOH of 9p.
Molecular studies: An NGS -based 400 gene somatic mutational panel (with a matched normal to exclude germline variants) identified mutations in: MYC, ID3, ARID1A, CCND3, FBXO11, CD28, and IGF1R. Comparison of variant frequencies (VF) suggested that the ID3 nonsense mutation, located on 1p36, demonstrated LOH, supported by the SNP-array result. An NGS – based RNA-fusion panel (targeting 199 genes, including exons of MYC) was negative for gene fusions. Clonal rearrangement of the Ig heavy chain gene was detected.
Proposed diagnosis: Burkitt lymphoma lacking MYC rearrangements and 11q aberrations, with ID3, CCND3, MYC, and ARID1A mutations in bone marrow
Interesting feature(s) of submitted case: This case of Burkitt lymphoma (BL) is unusual for its BM presentation in an immunocompetent patient. In addition, it is unique because the hallmark cytogenetic abnormality t(8;14)(q24;q32) and its variants, which juxtapose the MYC oncogene with one of the three Ig loci, could not be demonstrated in this tumor. Uniform MYC expression by IHC suggests an alternative mechanism of MYC upregulation. With the help of a large NGS-targeted panel, in addition to missense mutations in MYC, we identified mutations in ID3, ARID1A, and CCND3, which have been previously described in BL harboring canonical MYC rearrangements. It has been suggested that cooperation between ID3 inactivation and Ig-MYC translocation is a hallmark of BL lymphomagenesis. LOH at the mutated ID3 locus in our case may be illustrative of the importance of loss of ID3 function in lymphomagenesis, even in the absence of the classic MYC gene alterations that lead to MYC overexpression. To the best of our knowledge, no case has been reported in the literature with similar features.

EAHP18-BMWS-429

Nodular Lymphocyte Predominant Hodgkin Lymphoma presenting in the bone marrow

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Case description: A 68 year old man presents with weight loss, pancytopenia, splenomegaly and lymphadenopathy. A CT scan revealed portal hypertension, cirrhosis of the liver and lymphadenopathy above and below diaphragm. There were no palpable peripheral nodes. A PET CT scan highlighted PET avid lymph nodes in addition to avidity in thoracic vertebra. A full blood count revealed mild neutropaenaia and moderate thrombocytopenia with a normal haemoglobin.
Biopsy fixation details: 10% buffered formalin
decalcification 5% formic acid
Frozen tissue available: No
Details of microscopic findings: A hypercellular trephine biopsy containing a multifocal nodular lymphoid infiltrate associated with an increase in reticulin. The infiltrate consists of a small number of atypical large cells some of which display the morphology of LP cells in a background of small lymphocytes. Overall the lymphomatous infiltrate accounts for 90% of the cellularity.
Immunophenotype: The large cells co-express CD20,CD45,CD75,bcl6, PAX5, OCT2 and BOB1 and are negative for CD10,CD15,CD30 and EBV(ISH). The background small lymphocytes are predominantly of T lineage although a small number of small B cells are present within the nodules. A large number of PD1 positive cells and a lesser number of CD57 positive T cells are present with many forming rosettes around the large B cells.
Cytogenetics: Not available
Molecular studies: Not performed.
Proposed diagnosis: Marrow involvement by Nodular Lymphocyte Predominant Hodgkin Lymphoma with a differential of T cell rich B cell Lymphoma.
Interesting feature(s) of submitted case: The presence of PD1+, CD57+ rosettes suggests the presence of a NLPHL like microenvironment' although the relative small B lymphocyte depletion is somewhat more suggestive of T cell rich large B cell Lymphoma. Are these conditions part of the same disease spectrum and should they be treated in a similar manner? This patient was treated with R-mini CHOP resulting in complete remission which is maintained at two years

EAHP18-BMWS-115

High grade B-cell neoplasm with leukemic presentation

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Case description: The patient is a 67 year-old man with a past medical history of prostatic carcinoma, who presented with malaise, fever and chills. He was found to have a leukocytosis and thrombocytopenia (WBC 101.76x10^9/L, HGB 13.4 g/dL, PLT 94x10^9/L). Review of the peripheral smear showed 81% abnormal lymphocytes, as described below. Abdominal imaging was negative for hepatosplenomegaly but did show indeterminate liver lesions. There was no evidence of lymphadenopathy. Peripheral blood flow cytometry and bone marrow biopsy were performed.
After B-cell lymphoma was diagnosed, he was started on R-EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone). He responded well, and 3 months later peripheral blood and bone marrow aspirate and trephine showed no evidence of B-cell lymphoma.
Biopsy fixation details: The trephine biopsy was fixed in zinc formalin and decalcified with hydrochloric acid/EDTA. The clot section fixed was in zinc formalin.
Frozen tissue available: None
Details of microscopic findings: The peripheral leukocytosis was composed of intermediate to large cells with scant to moderate cytoplasm, irregular nuclear contours, finely dispersed chromatin, and small nucleoli. The bone marrow aspirate showed numerous similar cells. Examination of the bone marrow trephine showed effacement of normal hematopoietic architecture by a diffuse infiltrate of mononuclear cells. These were also intermediate to large in size with irregular nuclear contours, fine chromatin, and small visible nucleoli. Mitoses were apparent
Immunophenotype: By flow cytometry the B-cells displayed an abnormal immunophenotype, and expressed CD5,CD19, CD20, CD22 (dim), CD38, CD45, CD79b, FMC7 and monotypic kappa surface immunoglobulin light chains. The B-cells were negative for CD3, CD4, CD7, CD8, CD10, CD11b, CD13, CD14, CD16, CD33, CD34, CD56, CD64, CD65, CD123, and lambda.
Immunohistochemical stains showed the atypical B-cells were positive for CD20, BCL2, and MUM1. They were negative for CD3, CD10, BCL6, CD30, cyclin D1 and SOX11. LEF1 was positive in a subset of cells. MYC was positive in <40% of cells, and Ki67 was positive in approximately 80%.
Cytogenetics:
48,XY,inv(1)(p36.3q25),add(3)(p21),add(9)(p22)x2,add(10)(q26),del(11)(q21),+12,der(13)t(1;13)(q21;p11.2),-14,+mar1,+mar2[11]/46,XY[11]
Molecular studies: BCL2 translocation (FISH): Negative
BCL6 translocation (FISH): Negative
MYC translocation (FISH): Negative
IGH/MYC translocation (FISH): Negative
Proposed diagnosis: High grade B-cell neoplasm with leukemic presentation.
Interesting feature(s) of submitted case: This is a case of a high grade B-cell neoplasm of non-germinal center phenotype (by the Hans classifier) primarily presenting in the peripheral blood and bone marrow. Leukemic presentation is uncommon for high grade B-cell neoplasms, and is represented in the literature primarily as case reports. Although this case had some blastoid features, blastoid mantle cell lymphoma (cyclin D1-positive or -negative) was excluded, and there was also no evidence of BCL2, BCL6 or MYC translocation, although there was a complex karyotype. The patient responded well to chemotherapy, although follow-up to this point has been brief.

EAHP18-BMWS-116

A bone marrow presentation of high-grade B cell lymphoma with MYC and BCL2 rearrangements

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Case description: Patient presenting with six week history of malaise. Pancytopenia on full blood count and circulating blasts on examination of peripheral blood. Tumour lysis syndrome treated with intravenous fluid infusion and rasburicase. Flow cytometry suggestive of high-grade lymphoma and generalised lymphadenopathy subsequently discovered on CT imaging.
Biopsy fixation details: 10% neutral buffered formalin with chemical decalcification prior to processing.
Frozen tissue available: No.
Details of microscopic findings: Haemopoietic tissue is nearly completely effaced by sheets of large blasts with hyperchromatic nuclei containing multiple fine nucleoli. These are admixed with apoptotic bodies. Reticulin is densely increased in association with the infiltrate.
Immunophenotype: Expression of CD20, CD79a, CD10 and BCL2 within the infiltrate. There is expression of BCL6 in >50% of cells and weak-moderate CMYC expression in approximately 40% of cells. Ki67 labels at least 80% of cells.
Cytogenetics: MYC and BCL2 gene rearrangements identified on fluorescent in situ hybridisation performed on peripheral blood.
Molecular studies: Not applicable.
Proposed diagnosis: High-grade B cell lymphoma with MYC and BCL2 rearrangements
Interesting feature(s) of submitted case: Initial clinical presentation more suggestive of leukaemia than lymphoma.

EAHP18-BMWS-144

Bone marrow presentation of transformed lymphoplasmacytic lymphoma

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Case description: A 66 year old male presented with dyspnea, excessive sweating, and left upper abdominal discomfort. On physical examination, he was found to have lymphadenopathy above and below the diaphragm, and splenomegaly. His hemoglobin level was 10 gm/dl, WBC- 20.3 x 10^3/ul, platelets- 181 x 10^3/ul. Rouleaux formation and abnormal lymphocytes were noted on the peripheral blood smear. His LDH level was over 1000 U/L. Serum protein electrophoresis (SPEP) showed a monoclonal spike of IgMK of 4.1 gr/dl.
The patient was started on plasmapheresis therapy for hyperviscosity syndrome, with good results. The bone marrow biopsy (see below) showed a process most consistent with a transformed lymphoplasmacytic lymphoma. A subsequent lymph node biopsy showed a similar process.
The patient was treated with six cycles of R-CHOP and CNS prophylaxis with methotrexate. PET/CT scan at the end of therapy showed no clinical evidence of disease. A repeat bone marrow biopsy after therapy showed no evidence of large cell lymphoma; several small clusters of kappa-positive plasma cells, < 5% of the marrow, were present.
Biopsy fixation details: The bone marrow biopsy was fixed in 4% buffered formalin. This was followed by rapid acid decalcification, prior to embedding in paraffin.
Frozen tissue available: Frozen tissue was not obtained.
Details of microscopic findings: The overall cellularity is estimated at 80%, and the myeloid:erythroid ratio is estimated at 1:1 Trilineage hematopoiesis is present.
In addition to the cells of normal hematopoiesis, two additional populations of cells are present in the marrow: (1) A population of large lymphoid cells, and (2) a population of plasma cells. Several cells with intracytoplasmic and intranuclear inclustions are present.
Immunophenotype: On flow cytometry from the bone marrow aspirate, two populations of cells were seen. The first was a population of large lymphocytes, positive for CD19, CD20, and kappa light chains, and negative for CD5, CD10, CD23, and lambda light chains. The second population was one of plasma cells, positive for CD38, CD138, and kappa light chains, and negative for CD19 and lambda light chains.
Similar results were obtained with immunoperoxidase stains of the bone marrow biopsy. There is a population of large cells which are positive for CD20 and negative for CD3. In addition, there is a CD138+ population of plasma cells, which are clonal for kappa light chains.
Cytogenetics: Cytogenetic studies showed a complex karyotype, including +7, +8, -17.
Molecular studies: Molecular studies were postive for the MYD88 mutation.
Proposed diagnosis: Initial presentation of lymphoplasmacytic lymphoma in a transformed state.
Interesting feature(s) of submitted case: Diffuse large B-cell lymphoma (DLBCL) develops in approximately 4% of patients with lymphoplasmacytic lymphoma (LPL) after ten years (Am J hematol 91: 1032-1035, 2016). It is even rarer for LPL to exist simultaneously or present with DLBCL. We believe that this is an interesting case because the patient had the clinical findings of Waldenstrom's macroglobulinemia/ LPL, yet the bone marrow morphology was one of plasma cells with large, as opposed to small, lymphoid cells. The patient was not known to have LPL in the past. The positive MYD88 mutation would also be consistent with an underlying LPL process. We therefore believe that this case represents initial presentation of a transformed LPL process, with the initial diagnosis being made from the bone marrow examination.

EAHP18-BMWS-177

Large B-cell lymphoma with primary bone marrow presentation and possible hemophagocytic lymphohistiocytosis

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Case description: A 77-year-old male with a new diagnosis of prostatic adenocarcinoma presented with fever, acute urinary tract infection and pancytopenia. He had lost 25 pounds in the last three months. No lymphadenopathy was appreciated on physical exam. However, CT scan revealed new splenomegaly that was not seen on a scan from 6 months prior (15 cm). Serum ferritin level was markedly elevated (6870 mcg/L), as was lactate dehydrogenase (1995 U/L). Peripheral blood (PB) flow cytometry revealed a small kappa light chain restricted B-cell population. Bone marrow (BM) biopsy was performed and diagnosed as large B-cell lymphoma with rare hemophagocytic histiocytes present. Due to his critical condition, a trial of rituximab with high dose methylprednisolone was given. However, the patient quickly decompensated with DIC and died six days later.
Biopsy fixation details: B5/decalcification.
Frozen tissue available: No.
Details of microscopic findings: PB shows pancytopenia with circulating medium to large atypical lymphocytes with reticular chromatin, and moderate amount of gray blue cytoplasm. BM aspirate is sparsely cellular with scattered hematopoietic precursors and no increase in blasts. Atypical lymphocytes are present with similar morphology to that in the PB. Rare histiocytes with ingested erythrocytes are presented. BM biopsy shows hypercellularity with an interstitial infiltrate of large lymphocytes involving 20-30% of cellularity. Areas suggestive of intrasinusoidal growth are seen.
Immunophenotype: Large B cells express CD20, PAX5, MUM1, and MYC. They are negative for CD3, CD5, CD10, BCL2, BCL6 and EBV-ISH.
Cytogenetics: 46,XY[20]. Negative MYC breakapart probe.
Molecular studies: N/A
Proposed diagnosis: Large B-cell lymphoma with primary bone marrow presentation.
Interesting feature(s) of submitted case: This case demonstrates a large B-cell lymphoma with primary BM presentation in an elderly male who presented with pancytopenia. Aggressive, bone marrow-based lymphomas are often challenging to diagnose because of subtle morphologic features and lack of lymphadenopathy. Although some circulating atypical cells may be seen, as with this patient, these cells are often relatively few in number and not diagnostic. Pancytopenia is not a common presenting symptom of lymphoma, especially in the absence of marrow replacement. In this case the pancytopenia was an initial confounding factor and raised the possibility of hemophagocytic lymphohistiocytosis (HLH) (not definitively proven in this patient), as well as an acute leukemia prior to the diagnosis of lymphoma.
It is unclear if the patient's splenomegaly was due to lymphomatous involvement, HLH or other disorders. Given the somewhat intrasinusoidal growth pattern in the marrow, it is possible this represents transformation of an underlying splenic marginal zone lymphoma although the rapid development of splenomegaly would argue against the current lymphoma having transformed from a previously existing splenic low grade lymphoma. More likely we feel that this case represents the rare entity of a primary bone marrow lymphoma.

EAHP18-BMWS-187

De novo CD5+ diffuse large B-cell lymphoma with primary bone marrow presentation

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Case description: A 70-year-old male with a history of melanoma status post resection and atrial fibrillation on warfarin, presented with progressive fatigue and decrease in appetite for two months. Complete blood count showed leukocytes 29 x10^9/L with lymphocytes of 72%, hemoglobin 12.4 g/dL, and platelet count 184 x10^9/L. Serum LDH was significantly elevated at 7648 U/L. A bone marrow biopsy was performed.
Biopsy fixation details: 10% Buffered formalin
Frozen tissue available: No
Details of microscopic findings: Abnormal infiltrates of intermediate to large-sized cells were present (80% of the total marrow cellularity), with an intrasinusoidal pattern. The neoplastic cells had irregular nuclear contours, distinct nucleoli and moderate amounts of cytoplasm.
Immunophenotype: Flow cytometric analysis showed the neoplastic cells were positive for CD5, CD19, CD20, CD22 and CD38, and they were negative for CD10, CD11c, CD23, CD103 and CD200. Immunohistochemical studies revealed the neoplastic cells were positive for BCL2, and MUM1, and they were negative for BCL6, cyclin D1, MYC, SOX11 and Epstein-Barr virus encoded RNA (EBER).
Cytogenetics: FISH studies showed normal limits for the MYC, TP53, and CCND1 and IGH gene regions. Chromosomal microarray revealed a complex molecular karyotype with numerous regions of chromosomal gains and losses. Chromosomal gains included gain of 1p36.12-1p36.11, 3q21.2-3q29 (including BCL6), and 18q21.2-18q23 (including BCL2). Chromosomal losses included loss of 2q11.2-q12.1 and 2q22.1-2q24.3, 3p26.3-3p25.3 (including FHIT), 6q21 (including PRDM1), 9p21.3 (including CDKN2A/B), 10q23.1-10q23.31 (including PTEN), 16p13.3 (including a partial deletion of CREBBP), and a 1.3 Mb nested deletion at 5q23.2 with no known clinically relevant genes. A series of complex gains and losses were observed within 19q13.2-q13.43.
Molecular studies: None
Proposed diagnosis: De novo CD5+ diffuse large B-cell lymhoma (DLBCL)
Interesting feature(s) of submitted case: De novo CD5+ DLBCL is a rare subset of DLBCL with distinct clinicopathological and genetic features. It usually occurs in older females with an aggressive clinical course. Bone marrow involvement in an intravascular/intrasinusoidal infiltrative pattern is frequently seen. The majority of cases have non-germinal center B-cell phenotype and complex cytogenetic aberrations, including loss of 9p21 and gain of 19q13, which were identified in this case. De novo CD5+ DLBCL is different from Richter's transformation of CLL/SLL, mantle cell lymphoma, secondary CD5+ DLBCL and intravascular large B-cell lymphoma. The subsequent splenic biopsy on this patient revealed CD5+ DLBCL involvement without an intravascular/intrasinusoidal pattern, making the diagnosis of intravascular large B-cell lymphoma unlikely.

EAHP18-BMWS-212

Primary lymphoma of bone, mimicking myeloma : A case report and review of literature

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Case description: 66 -years old male presented with severe pain in the left hip for two months associated with weight loss. Physical examination revealed a bed bound patient due to severe left hip pain. Bilateral hips tenderness with limited range of movement, no organomegaly. Investigations showed serum calcium 2.97mmol/L (2.1-2.55mmol/L), albumin 26gm/L (35-50gm/L), LDH 438 U/L(125-220). Beta-2 macroglobulin 3.64 mg/L(0.87-2.64), urine is negative for bence-Jones Protein, serum protein electrophoresis showed no monoclonal band, Ka FLC 99.4(3.3-19.4), La FLC 24.9 (5.71-26), Ka/La FLC ratio of 3.98 [0.26-1.65]. MRI spine thoracic lumbar showed extensive involvement of bone marrow of the vertebrae with low signal in T1 WI and high signal in STIR images. Variable degree of vertebral collapse more marked at T7 and L4 (yellow arrows). PET CT scan showed moderate to intense uptake in multiple lytic lesions associated with cortical breakdowns scattered widely in the imaged skeleton involving vertebrae, ribs, clavicles, scapulae, pelvic bones, and proximal 2/3 of humeri and both femora down to the knees reported as compatible with extensive multiple myeloma.
Biopsy fixation details: Paraffin embedded biopsy fixed in AZF.
Frozen tissue available: NA
Details of microscopic findings: Peripheral blood shows mild hypochromic microcytic anemia, Hb (10.8 g/dl), mild thrombocytosis (Platelets: 430 x10^3/ul) and mild leukocytosis (WBCs: 11.310^3/ul) with leucoerythroblastic picture. Bone marrow aspirate is partially hemodilute shows relative increase in lymphocytes (52%) that appear mature looking, few (4%) looks atypical with blastoid morphology. Touch slides is hypercellular and stuffed with many medium to large cells with very high N/C ratio, irregular nuclear borders, some show blastic morphology. Bone marrow biopsy appeared hypercellular for age with ~ (75% to 85%) and extensively infiltrated by medium to large sized abnormal cells, with irregular nuclear contour, some with blastic morphology with marked depression of the trilineage hematopoietic cells and showed diffuse positivity for CD20, PAX5, CD10, Bcl6, partial Bcl2 and shows >90% positivity for Ki67 and (20% to 30%) positivity for C-MYC, while negative for CD34, TdT, CD5 and CD23 with reactive increase in CD3 positive T-cells. There is significant increase in reticulin fibers (Grade 2/3).
Immunophenotype: Flow cytometry on bone marrow aspirate shows a minute population of monotypic B cells comprises < 1% expressing CD19, CD20, CD10, FMC7, CD11c, cBCL2, partial CD43, IgM and show Kappa light chain restriction. The cells are negative for CD79b, CD5, CD23, CD103, CD200, IgD, IgG and IgA.
Cytogenetics: Cytogenetic study revealed abnormal karyotype:
47,XY,+X,t(1;3)(q42;q12),add(14)(q32),add(19)(q13.3)[7]/46,XY[43].
Molecular studies: NA
Proposed diagnosis: Primary bone and bone marrow B cell lymphoma with multiple lytic bone lesion.
Interesting feature(s) of submitted case: Our case presented with extensive multiple lytic bone lesions mimicking plasma cell myeloma, while marrow examination showed extensive bone marrow infiltration by lymphoma cells with very high ki67 proliferation index. Primary lymphoma of the bone is exceeding rare and its radiological findings are variable and nonspecific, therefore accurate diagnosis without pathology is quite difficult and when radiologically diagnosing bone tumors, the possibility of primary bone lymphoma should be considerd.

EAHP18-BMWS-214

CD30-positive diffuse large B-cell lymphoma presenting in bone and bone marrow

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Case description: The patient is a 67 year old man, evaluated 2 weeks prior at a local hospital for worsening pain in his right upper quadrant and thorax. He had no abnormal findings by CT or ultrasound and was released with pain medications. A MRI study, performed one week later, showed multiple enhancing lesions in the lumbar spine and pelvis, as well as enhancement of the marrow in multiple thoracic and lumbar vertebrae. He came to our institution for further evaluation.
Upon physical exam, no lymphadenopathy or organomegaly was appreciated.
No serum IgG, IgA or IgM elevations or monoclonal gammopathy by serum protein electrophoresis were identified.
Additional imaging studies were performed, confirming multiple lytic lesions throughout the vertebrae. A FDG PET/CT was also performed. Multiple lesions were highlighted in the left occipital bone, T4, T6, L2, ribs, sacrum and right acetabulum, with SUV ranging from 11.1 to 28.8. No FDG avid lymph nodes were highlighted.
At our institution, he underwent needle biopsy and fine needle aspiration of a L3 lesion; however, the samples were not diagnostic. Bilateral bone marrow samples were then collected.
Biopsy fixation details: 10% formalin buffer
10% Formalin buffer
Frozen tissue available: None available
Details of microscopic findings: In the BM biopsy sample from the left iliac crest, the cellularity was estimated at 80 to 90%. Multifocal, ill-defined aggregates of atypical cells were noted, replacing up to 50% of the medullary space. The atypical cells are large, with vesicular chromatin, multiple nucleoli and abundant cytoplasm. Many cells showed nuclear irregularities/folding, though multlobulated or multiinucleated forms were not appreciated. These cells are in a background of small lymphocytes and histiocytes. No associated necrosis is appreciated. In medullary areas not involved by lymphoma, trilineage hematopoiesis is noted. These cells were not definitively identified in the aspirate smear or touch imprint slides.
Immunophenotype: By immunohistochemical staining, the neoplastic cells are positive for CD20, PAX5, CD30, CD45(LCA), BCL2, BCL6(dim), MUM1 and OCT2 and are negative for CD3, CD10, CD138, BOB1 and EBER. The proliferation rate of the neoplastic cells by Ki-67 staining was high (~90%).
Cytogenetics: Not performed
Molecular studies: Not performed
Proposed diagnosis: CD30-positive diffuse large B-cell lymphoma in bone marrow
Interesting feature(s) of submitted case: The presentation of this lymphoma in bone, without lymphadenopathy/organomegaly by physical exam or by radiographic evidence of lymph node or other organ involvement, is unusual. The morphologic features of the neoplastic cells raises the possibility of high grade/large B-cell lymphoma or classical Hodgkin lymphoma. The immunophenotypic features are more consistent with large B-cell lymphoma, despite the CD30 expression. The pattern of positive immunohistochemical staining confims that the lymphoma forms groups and clusters supporting diffuse large B-cell lymphoma in bone marrow. This lymphoma has a non-GCB phenotype, using the classification system described by Hans and colleagues.
CD30 expression has been reported to occur in 14 to 25% of DLBCL cases and to confer a more favorable prognosis in R-CHOP treated patients, specifically superior overall survival (5-year OS: 79% in CD30+ DLBCL vs. 59% in CD30- DLBCL) and progression free survival (5-year PFS: 73% in CD30+ DLBCL vs. 57% in CD30- DLBCL) The majority (85%) of CD30+ DLBCL cases are reported to be nodal (75%) and to have centroblastic morphology, with 12% showing pleomorphic/anaplastic morphology. CD30 expression is more frequent in DLBCL without MYC rearrangement.

EAHP18-BMWS-215

Intravascular Large B-cell Lymphoma with Bone Marrow Presentation.

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Case description: 74 year old woman with history of diabetes presented 6/6/2017 at our institution with progressive weakness, fatigue, and anemia. She denied fever, chills, or weight loss. Her anemia was first noted in April 2017. Outside workup showed elevated LDH and IgM lambda monoclonal gammopathy. CT did not detect lymphadenopathy or organomegaly. Her admission labs showed a hemoglobin level of 5.2 g/dL and features of hemolysis including elevated LDH, decreased haptoglobin, and dark colored urine. She was transfused with PRBC. No lymphadenopathy, skin lesions, or focal neurologic abnormalities were noted. A repeat bone marrow biopsy was performed. Following her diagnosis, the patient was initiated on R-CHOP on 6/12/2017 with good response. She continued her chemotherapy locally. MRI performed a month later showed no CNS involvement. Her last follow-up from 8/3/2017 indicated symptomatic improvement and plans to continue R-CHOP chemotherapy as well as initiation of methotrexate CNS prophylaxis.
Biopsy fixation details: B5/decalcification.
Frozen tissue available: None.
Details of microscopic findings: CBC (6/7/17): Hgb 7.3 g/dL; RBC 2.30 x10(12)/L; MCV 97.8 fL; RDW 21.1%; WBC 4.3 x10(9)/L; PLT 101 x10(9)/L. Differential %: neutrophils 60; lymphocytes 28; monocytes 10; basophils 2. The peripheral blood smear showed slight polychromasia and spherocytosis, but is otherwise unremarkable. The bone marrow aspirate was suboptimal due to crush artifact. The core biopsy was markedly hypercellular (90%), and was focally involved by an abnormal sinusoidal infiltrate of intermediate-sized to large lymphoid cells open chromatin and multiple small nucleoli, in a background of morphologically unremarkable trilineage hematopoiesis. Plasma cells were not increased.
Immunophenotype: Flow cytometry: Negative.
Immunohistochemical studies: Positive for CD20, CD5 (weak), BCL2, MUM1, and MYC (50-60%); negative for CD2, CD3, CD7, CD10, CD30, ALK1, BCL6, cyclin D1, and SOX11.
In situ hybridization for EBV encoded RNA (EBER): Negative.
Cytogenetics: Normal FISH study for MYC.
Molecular studies: Not performed.
Proposed diagnosis: Intravascular large B-cell lymphoma, with isolated bone marrow involvement.
Interesting feature(s) of submitted case: Intravascular large B-cell lymphoma is an aggressive subtype of large B-cell lymphoma characterized by selective intravascular growth, usually presenting with wide dissemination in extranodal sites including the bone marrow. Lymph nodes are usually uninvolved. There are two major forms differed by clinical presentation. The classic/Western form is characterized by predominant neurologic and dermatologic manifestations, where central nervous system is involved in most cases. The Asian form is characterized by hemophagocytic syndrome, multiorgan failure, hepatosplenomegaly, and pancytopenia. B symptoms are comment in both forms. CD5 expression is fairly common (40%). This case is unusual due to the isolated bone marrow involvement without extramedullary disease or B symptoms at presentation, suggesting early manifestation by this typically aggressive lymphoma. Although secondary bone marrow involvement by another large cell lymphoma such as diffuse large B-cell lymphoma or splenic B-cell leukemia/lymphoma undergoing large cell transformation have also been considered, the exclusively intravascular pattern, and absence of lymphadenopathy and splenomegaly are not supportive of these possibilities.

EAHP18-BMWS-229

Aggressive large B-cell lymphoma of bone marrow with initial presentation as hemophagocytic syndrome

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Case description: 66-year-old man with medical history of type II diabetes mellitus and hypertension presented with progressive abdominal pain, daily fevers, drenching sweats, and weight loss.
Laboratory studies showed thrombocytopenia and anemia. There was massive splenomegaly on CT imaging. Ferritin was elevated at 44,712 ng/mL (normal range 22-322 ng/mL). Hemophagocytic syndrome was suspected. A splenectomy was performed which showed congestive splenomegaly followed by bone marrow biopsy a month later.
Biopsy fixation details: Bone marrow trephine biopsy was placed in 10% buffered formalin and allowed to fix for 8 hours.
Frozen tissue available: NA
Details of microscopic findings: The bone marrow biopsy showed an average cellularity of 50% (ranging from 30% to 65%). There was a focal cluster of large atypical cells with high nuclear to cytoplasmic ratio, large irregular nuclei, and vesicular chromatin with prominent nucleoli. Outside this focus of cells, there were abundant macrophages with a background of minimal residual trilineage hematopoiesis and mild fibrosis.
Immunophenotype: The large atypical cells were positive for CD20, BCL6 and MUM1 while negative for CD10 and CD30. Ki-67 was approximately 95%.
Flow cytometry analysis of the bone marrow aspirate showed no evidence of a clonal B-cell population (normal marrow, sampling artifact).
Cytogenetics: NA
Molecular studies: NA
Proposed diagnosis: Diffuse large B-cell lymphoma (DLBCL), high grade, non-germinal center type (favor bone marrow-liver-spleen type of LBCL)
Interesting feature(s) of submitted case: This case is unique in that it represents a rare aggressive form of large B-cell lymphoma (LBCL) with primary bone marrow presentation, associated with hemophagocytic syndrome. This case's distinctive clinical presentation with no involvement of blood, lymph node or other extranodal sites is consistent with the recently-described unusual subtype of LBCL designated as "bone marrow-liver-spleen" (BLS) type of LBCL.
A series of 11 cases published by Yeh et al. in 2010 described the BLS type of LBCL as an aggressive form of LBCL, which usually presented with fever and hemophagocytic syndrome. Bone marrow examination showed patchy and interstitial infiltration of large B cells without sinusoidal involvement. Like in this case, all cases had a high Ki-67 index (≥90%), and a non-germinal center/activated B-cell immunophenotype was common. In addition, all cases were negative for Epstein–Barr virus and human herpesvirus 6 and 8.
BLS type of LBCL has an unusual presentation suggestive of an infectious etiology, which may lead to diagnostic delays. In addition, bone marrow infiltration is usually patchy, adding to the diagnostic challenge. Prognosis is poor. Prompt diagnosis with aggressive management may prolong survival.
In this case, the treatment plan included six cycles of R-CHOP. At three months after diagnosis, four cycles had been completed with resolution of the hemophagocytic syndrome after initiation of treatment.

EAHP18-BMWS-267

46-year-old woman with refractory leukemia/lymphoma with complex cytogenetics.

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Case description: A 46-year-old woman presented with leukocytosis, anemia and retroperitoneal lymphadenopathy. She was diagnosed with Burkitt-like lymphoma, treated with EPOCH and transferred for further care. On admission, her WBC was 24.4 k/uL, Hgb 6.9 mg/dl, platelets 248 K/uL. Bone marrow biopsy (12/2016) showed extensive involvement by a high-grade lymphoma/leukemia. Since flow cytometry showed CD45dim, TdT positive forms B lymphoblastic leukemia treatment was instituted. After 3 cycles of HyperCVAD her bone marrow demonstrated complete morphologic and cytogenetic remission (3/2017). One week prior to bone marrow transplant, she presented with back pain and atypical cells. Repeat bone marrow (5/2017) revealed molecular relapse. Rituximab/ICE was started; Few days later imaging studies revealed bowel wall thickening and mesenteric lymphadenopathy. Biopsy of a lymph node confirmed recurrent high-grade lymphoma/leukemia. She was treated with EPOCH, DHAP and later with Bendamustine and Velcade. She is alive, 13 month after initial diagnosis, awaiting CAR-T cell treatment.
Biopsy fixation details: Bone marrow biopsies were fixed in AZF and decalcified. Lymph node tissue was fixed in formalin.
Frozen tissue available: None
Details of microscopic findings: Diagnostic bone marrow (12/2016) was hypercellular (>90%) with diffuse involvement by leukemia/lymphoma and minimal residual hematopoiesis. Infiltrating lymphocytes were intermediate with high NC ratio, fine chromatin, indistinct nucleoli and high mitotic activity.
Lymph node biopsy (8/2017) at relapse showed neoplastic cells similar to that at presentation.
Immunophenotype: Diagnostic bone marrow flow cytometry: Abnormal CD45dim population (84% of total) positive for CD19, CD10, HLA-DR, and TdT(subset); negative for CD34, CD20, surface light chains, T-cell and myeloid markers. Immunohistochemistry: Neoplastic cells were positive for CD38, BCL2, PAX5, MUM1, CMYC, CD10, TDT(small subset) and negative for BCL6, CD20, CD34, cKIT, T-cell markers.
Lymph node at relapse: Similar to that at presentation. TdT was negative.
Cytogenetics: Bone marrow:
48,XX,t(4;12;7)(q33;q15;q22),add(6)(q25),+7,t(8;22)(q24;q11.2),+der(12)t(4;12)(q33;q15), t(14;18)(q32;q21)[8]/48,idem,+X,-add(6)(q25),+6,-der(12)t(4;12),-14,+der(14)t(14;18),add(16)(p13.3)[3]/46,XX[4].nuc ish(cMYCx2)(5'cMYC sep3'cMYCx1)[43/50],(IGH,BCL2)x3(IGH con BCL2 x2)[49/50]
FISH: cMYC rearrangement and t(14;18)
Molecular studies: Lymph node at relapse: Genomic alterations include BCL2, KRAS Q61L, CCND3 1209K, CDKN2A/B loss, HIST1H2AM Q105fs*8, MLL2 R2410*
Proposed diagnosis: High-grade B-cell leukemia/lymphoma with t(14;18) and 8q24/MYC rearrangements and complex karyotype. (WHO High-grade B-cell lymphoma with MYC and bcl2 rearrangements).
Interesting feature(s) of submitted case: This case meets diagnostic criteria for WHO high-grade B-cell lymphoma with MYC and bcl2 rearrangements. However, flow cytometry at presentation showed dimCD45 and presence of TdT in a subset of cells and immunohistochemistry identified rare TdT positive forms. Given TdT expression B lymphoblastic protocol was used as one of the treatment modalities during the course. Currently presence of TdT discriminates between mature and lymphoblastic phenotype in high grade B-cell lymphomas. However, interpretation of TdT by flow cytometry and in decalcified bone marrow can be difficult making distinction of mature versus lymphoblastic neoplasms challenging. Unfortunately this tumor did not respond to any known treatment.

EAHP18-BMWS-275

High-grade B-cell lymphoma with MYC and BCL2 rearrangements in a staging marrow for a newly-diagnosed low-grade follicular lymphoma; high-grade B cell lymphoma appears primarily bone marrow-based by PET/CT

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Case description: A 54 year-old man with rheumatoid arthritis (RA)(diagnosed at 27y/o) presented with lymphadenopathy, night sweats and fever. Treatment for RA including methotrexate and abatacept was discontinued in June 2017. Right axillary lymph node (LN) biopsy performed one month later showed follicular lymphoma, grade 1-2 of 3. Flow cytometric studies performed on the LN showed a CD10 positive monotypic B cell population expressing surface kappa light chain. Karyotyping on the LN showed 46,XY,t(14;18)(q32;q21)[6]/46,XY[4]. CBC: Hgb: 11.3 g/dl, Hct: 34.2%, MCV: 83.5fl, Plt: 441 K/ml, WBC: 10.9 K/ml (N/bands:64%,L:21%,M:9%,Eos:2%, Baso:1%,Myelo:1%, Meta:2%).
Biopsy fixation details: B+ fixative and Ion-Exchange Decalcification were used.
Frozen tissue available: N/A
Details of microscopic findings: The staging bone marrow (BM) biopsy showed a hypercellular marrow with a significant portion replaced by medium to large lymphoid cells that were mostly diffuse but focally paratrabecular. Mitotic figures and apoptosis were readily identified. Large areas of coagulative necrosis were noted. In the uninvolved marrow, maturing trilineage hematopoiesis was identified with no significantly increased blasts.
Immunophenotype: Flow cytometric studies performed on the aspirate demonstrated a CD10 positive monotypic B cell population expressing surface kappa light chain (2.9% of the cells) with high forward scatter consistent with large cell size. Also present were very few polytypic background B cells (0.7% of the cells) and very few maturing hematogones (0.9% of the cells). In the biopsy, CD20 and PAX5 stain highlighted B cells accounting for ~50% of the marrow cellularity. The B cells were positive for CD10, BCL6, BCL2, MYC, negative for IRF4/MUM1, cyclin D1 and TdT. CD21 did not show significant follicular dendritic cell meshworks. Ki67 highlighted a high proliferation rate (focally 90%). EBV in situ hybridization and EBV LMP stain were negative.
Cytogenetics: Karyotype:46,XY,t(7;8)(p22;q24.1),t(14;18)(q32;q21),der(14)t(14;18)(q32;q21)[cp4]/46,XY[11]. FISH:nuc ish(BCL6x2)[207],(MYCx2)(5'MYC sep 3'MYCx1)[11/249],(5'IGHx2,3'IGHx2~3)(5'IGH con 3'IGHx1)[16/238],(BCL2x2)(5'BCL2 sep 3'BCL2x1)[9/232](MYC, BCL2 and IgH rearrangements were identified in similarly low percentage of cells, corresponding to the low percentage of neoplastic B cells in the aspirate)
Molecular studies: N/A
Proposed diagnosis: High-grade B cell lymphoma with MYC and BCL2 rearrangements, transformed from follicular lymphoma.
Interesting feature(s) of submitted case: This case demonstrated an unusual discordance between the tissue and the staging BM, different from the common scenario in which small B cell lymphoma is identfiied in BM in patients diagnosed with large B cell lymphoma. PET/CT studies in our patient confirmed the presence of high SUV lesions largely limited to the skeleton, suggestive of a primary BM presentation of the high-grade B cell lymphoma. Two different models of follicular lymphoma (FL) transformation have been reported based on the findings from whole exome sequensing and SNP array studies (Cell Rep. 16;6(1):130-140). Divergent evolution model in which FL and tFL (tranformed FL) derived from a common mutated precursor cell, instead of the linear model in which tFL originates directly from FL, seems to occur more frequently. The almost simutaneously diagnosed high-grade B cell lymphoma with MYC and BCL2 gene rearrangements and low-grade follicular lymphoma in our patient also favors a likely divergent evolution. The contributions of the patient's rheumatoid arthritis and methotrexate therapy which was only discontinued just prior to his initial biopsy are uncertain.

EAHP18-BMWS-286

High-grade B-cell lymphoma, NOS

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Case description: The patient is a 74 year old male with a past medical history of hypertension who initially presented with altered bowel habits. CBC revealed anemia (Hb 9g/dL), thrombocytopenia (82x10^9/L), and a WBC count of 11x10^9/L with a peripheral smear revealing numerous nucleated RBCs and rare atypical lymphocytes with deeply basophilic cytoplasm with vacuoles. CT scans of the head, chest, abdomen and pelvis were remarkable for iliac chain lymphadenopathy and splenomegaly. He underwent inguinal lymph node and bone marrow biopsy on the same day. The lymph node biopsy revealed a small B-cell lymphoma (kappa restricted, positive for CD19/20, and negative for CD5/10/43/cyclin D1), favored to be a nodal marginal zone lymphoma. He was treated with 6 cycles of DA-EPOCH with prophylactic intrathecal MTX and initially achieved complete remission. However, 3 months later, he relapsed with significant CNS involvement for which he was started on the IDARAM protocol with HD-MTX but subsequently progressed and was transitioned to hospice care.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: Not applicable
Details of microscopic findings: The aspirate smears demonstrate abundant blastoid lymphoid cells with small nucleoli and scant, deeply basophilic cytoplasm with numerous vacuoles. H&E sections of the core biopsy demonstrate extensive infiltration by a population of intermediate to large sized mononuclear cells with irregular nuclear contours, small nucleoli, and indistinct cell borders which occasionally overlap. Interspersed among the mononuclear infiltrate are numerous mitotic figures and abundant tingible body macrophages, imparting a "starry sky" background.
Immunophenotype: Positive: CD20, CD10, Ki-67(>95%); negative: CD3, CD5, BCL2, cyclin D1, TdT, CD34, EBER ISH
Cytogenetics: 47,XY,t(3:14)(q27;q32),del(6)(q13q24),+8,del(8)(q24),der(16)t(1;16)(q21;q24)[7];46,XY[13]
FISH:
nuc ish(BCL6x2)(5'BCL6 sep 3'BCL6x1)[34/200]
nuc ish(D8Z2x3,MYCx2)[200]
nuc ish(BCLx2)[200]
nuch ish(IGHx2)(5'IGH sep 3'IGHx1)[33/200]
nuc ish(MYCx2,IGHx3)[21/200]
Molecular studies: None performed
Proposed diagnosis: High-grade B-cell lymphoma, not otherwise specified
Interesting feature(s) of submitted case: This case is interesting in that it represents a rare and diagnostically challenging instance of a high-grade B-cell lymphoma with overlapping features between Burkitt lymphoma and DLBCL. On the bone marrow aspirate, the lymphoma cells exhibit classic Burkitt-like morphology with finely clumped chromatin, multiple small nucleoli and scant, deeply basophilic cytoplasm with vacuoles. On the bone marrow biopsy, while a classic “starry sky” background is present, many of the tumor cells are large with significant nuclear pleomorphism and contour irregularities, as well as crowded and occasionally overlapping cell borders. The germinal center immunophenotype could be consistent with either Burkitt or DLBCL. However, the complex cytogenetics, which include a BCL6-IgH translocation and trisomy 8 with one chromosome actually demonstrating a MYC deletion, do not support the diagnosis of Burkitt lymphoma. For these reasons, we felt the most appropriate diagnostic category currently available is the new WHO-defined entity high-grade B-cell lymphoma, NOS.
Also meriting attention in this case was the presence of a synchronous nodal marginal zone lymphoma, from which the high-grade lymphoma may have transformed.

EAHP18-BMWS-291

Intravascular large B-cell lymphoma presenting and diagnosed in the bone marrow

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Case description: 78-year old female of South Asian ethnicity presented with a three week history of high fevers. Laboratory examinations revealed pancytopaenia and high acute phase markers.
There was no skin rash.
Bone marrow trephine biopsy (sections submitted to workshop) appearances were interpreted as diffuse large B-cell lymphoma with features that raise the possibility of large B-cell lymphoma , but it was felt that the degree of extravascular infiltration may be slightly against this diagnosis.

Further information

A history of surgery for excision of a gastric gastrointestinal stromal tumour (GIST) two months previously was revealed. Review of this showed the following:
Confirmed the presence of a GIST within which were thin walled vessels distended by infiltration by large atypical CD20 positive B-cells. The infiltration was exclusively intravascular (images provided in power point presentation)
A random skin biopsy performed (despite the absence of skin lesions) showed no evidence of involvement (not submitted)
Biopsy fixation details: decalcification by EDTA. Formalin fixed paraffin embedded
Frozen tissue available: No
Details of microscopic findings: Hypercellular bone marrow for the age of patient with dyserythropoiesis and some megaloblastoid features. Megakaryocytes plentiful with some micromegakaryocytes. No increase in blasts. There is a population of large atypical anaplastic lymphoid cells present in clusters with the majority displaying an intravascular distribution. Definite evidence of haemophagocytosis not identified.
The marrow reticulin is increased (grade 2 of 3)
Immunophenotype: The population of large atypical lymphoid cells is highlighted by B-cell markers CD20 and CD79a. They are present in clusters many of which are distending sinusoids seen on single stains but also highlighted by double staining for CD34 and PAX5. However, there are some clusters and single cells that appear to be out-with vascular spaces. The atypical B-cells express BCL6, MUM1 and BCL2 and appear weakly positive for CD10. They express IgM, but are negative for IgD. A proportion is positive for CD30. They also express CD5 weakly (in contrast to strong CD5 expression in background T-cells) but are negative for CD23 and cyclinD1. MYC is positive in a proportion of the cells, but quantification is difficult. EBER is negative by in situ hybridisation. There a few groups of small CD20 positive B-cells, focally in the vicinity of the large cells. There is a mild increase in T-cells with some concentration around the large B-cells.
Cytogenetics: FISH studies for MYC, BCL2 and BCL6 rearrangements pending
Molecular studies: Not performed
Proposed diagnosis: Intravascular large B-cell lymphoma
Interesting feature(s) of submitted case: This case reiterates the clinical presentation in such cases with lack of lymphadenopathy or mass lesions. This patient who is of Asian ethnicity presented with pancytopaenia and systemic symptoms and lacked skin involvement, a clinical presentation that is more typical of the Asian rather than Western variant of intravascular large B-cell lymphoma. As is often in these cases, a high index of suspicion is required for diagnosis and immunohistochemistry is crucial to highlight the neoplastic infiltrate which may be overlooked /misinterpreted for haemopoietic blasts. Not surprisingly, the subtle exclusive intravascular large B-cell infiltrate present within the gastrointestinal stromal tumour (GIST) that was excised two months previously was overlooked.

EAHP18-BMWS-330

Marrow involvement by clonally-related chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and high grade B-cell lymphoma with MYC gene rearrangement

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Case description: 48 yo male previously diagnosed with CLL/SLL in 2006, treated with fludarabine, cyclophosphamide, rituximab, and ibrutinib. He presented with worsening autoimmune anemia, leukocytosis, and thrombocytopenia with poor response to transfusions, as well as highly elevated LDH and uric acid levels.
Biopsy fixation details: Formalin, decalcified
Frozen tissue available: N/A
Details of microscopic findings: The marrow is hypercellular (>95% cellularity), with extensive replacement by atypical lymphoid cells, and marked reduction in normal trilineage hematopoiesis. The majority of the lymphoid cells (~90% of cellularity) are intermediate to large-sized, monotonous appearing, with slightly irregular nuclei, fine to dispersed chromatin, variably distinct nucleoli, and small amount of cytoplasm. A small subset of lymphoid cells (~10% of cellularity) are small-sized, monotonous appearing, with round nuclei, clumped to condensed chromatin, indistinct nucleoli, and scant cytoplasm.
The peripheral blood smear shows a dimorphic atypical lymphocytosis with similar morphology as the bone marrow. There is normocytic, normochromic anemia with moderate anisopoikilocytosis, and marked thrombocytopenia.
Immunophenotype: 1. Small B-cell lymphoma flow cytometry: CD19 (subset dim), CD20 (dim), CD22 (dim), CD5 (subset+), CD23+, CD10-, FMC7-, CD38 (mostly absent), CD45 (dim), CD200 (bright), kappa light chain-restriction (dim). Immunostains: PAX5+, LEF1+, cyclinD1-, BCL6-, LMO2-
2. HGBL flow cytometry: CD19 (dim+), CD20-, CD22 (dim+), CD5-, CD23-, CD10+, FMC7-, CD38 (bright+), CD45 (dim+), CD200-, kappa light chain-restriction (dim). Immunostains: PAX5+, CD34-, TdT-, BCL2-, BCL6-, MUM1-, MYC (high), cyclinD1-
Cytogenetics: 1. Small B-cell lymphoma FISH: Loss of TP53 (17p13) in 85% of cells. No evidence of MYC (8q24) rearrangement. SNP array: Loss of 1q42.12-q43; Copy neutral loss of heterozygosity (CN-LOH) in 13q11-q14.2, 13q14.3-q34; homozygous deletion of SETDB2 (13q14.2) and hemizygous deletion of RB1 (13q14.2); Loss of 17p13.1-p12 including TP53; Gain of chr X.
2. HGBL FISH: MYC (8q24) rearrangement in 98% of cells. No evidence of TP53 (17p13) deletion. SNP array: Gain of chr 1, 22, and 8p terminal to 8q24.21; CN-LOH in chr 12, 13, and 17p terminal to 17p11.2, including TP53; homozygous deletion of 13q14.2, including RB1 and SETDB2.
Molecular studies: Using IGH gene rearrangement analysis by Next Generation Sequencing (NGS) with FR1 primers, a single clonal sequence was identified in the flow cytometry-sorted CD5+ kappa-restricted small B-cell population, sorted CD10+ kappa-restricted large B-cell population, and unsorted cell sample. The clonal sequence was identical in all 3 samples, with a 293bp PCR-amplified product, IGHV usage of V3-30, IGHJ usage of J4, and 0% IGHV mutation frequency (unmutated).
Targeted mutation detection by NGS method on unsorted cells showed the following variants: SF3B1 p.K666E, TP53 p.M237I, TP53 p.G244C, TP53 p.E271K, and RAD21 p.P616L
Proposed diagnosis: Bone marrow involvement by CLL/SLL, and high grade B-cell lymphoma (HGBL) with MYC gene rearrangement, clonally related
Interesting feature(s) of submitted case: The CLL/SLL and HGBL have different immunophenotypic profile, but are shown to be clonally-related by IGH gene rearrangement analysis, and share alterations in RB1, SETDB2, and TP53 genes by SNP array analysis. Based on the two tumors' clonal relationship yet markedly different immunophenotypic profile, we hypothesize that rather than a linear Richter's transformation, a common clonal progenitor with divergent clonal evolution might have given rise to the two different tumors at different time points.

EAHP18-BMWS-337

Intravascular large B-cell lymphoma presenting in the bone marrow

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Case description: 61-year-old man presented with syncope and 6 months of progressive weakness. New pancytopenia was noted and the patient was diagnosed with myelodysplastic syndrome (MDS-MLD). A small lambda clonal CD5+ CD20(bright)+ B-cell clone (1%) was detected by flow cytometry but it was not histologically evident in the marrow. Conventional cytogenetics on this bone marrow revealed: 46,XY,add(6)(q25),der(6;18)(p10;q10),del(13)(q12q22),+mar1x2[8]/46,XY[12]. CT scan showed mediastinal lymphadenopathy concerning for lymphoma. Patient developed fever and was empirically given multiple antibiotics but his clinical course worsened and he was intubated. Excisional biopsy of the mediastinal lymph nodes was performed and showed reactive lymph nodes and flow studies were negative for lymphoma. Concurrent fine needle aspiration (FNA) from a mediastinal lymph node was compatible with a reactive process however flow cytometry performed on the FNA specimen revealed a small clonal B-cell population with similar immunophenotype to the one seen on the bone marrow. Patient's clinical course worsened including poor mental status and he remained intubated. MRI and CT of the head showed no mass lesions. A repeat bone marrow biopsy was performed 5 weeks after original presentation for further evaluation.
Biopsy fixation details: The bone marrow core biopsy and the aspirate specimen were fixed in zinc formalin.
Frozen tissue available: No.
Details of microscopic findings: The aspirate smear is hemodilute, paucicellular, and aspicular. The majority of the cellularity consists of mature neutrophils and lymphocytes with occasional myeloid and erythroid precursors. Rare atypical large mononuclear cells with irregular nuclei, slightly condensed chromatin, prominent nucleoli, and moderate amounts of cytoplasm are seen. H&E and PAS stained sections show trabecular bone with extensive aspiration artifact and small amounts of apparently mildly hypercellular marrow (60%). Multiple clusters of large mononuclear cells with oval nuclei, vesicular chromatin, prominent nucleoli, and moderate amounts of cytoplasm account for approximately 20% of cellularity. At least some appear intravascular. The myeloid to erythroid ratio is 2:1. Erythroid elements are mildly increased and show orderly maturation. Myeloid elements are present in expected numbers and show orderly maturation. Megakaryocytes are present in expected numbers with dysplastic changes (hypolobation, senescent forms, micromegakaryocytes, widely spaced nuclear lobes).
Immunophenotype: Immunostains performed on the bone marrow core with adequate controls demonstrate multiple clusters of CD20+ CD79a+ MUM1+ CD5 (subset dim)+ CD10- BCL6 (subset dim)+ large B cells (approximately 20% of total cellularity).
Flow cytometry performed on the bone marrow aspirate demonstrated a minor clonal expansion (2% of total events) of large surface lambda restricted CD5 (dim)+ CD10- CD19(dim variable)+ CD20+ CD23+ CD38+ IgM(variable)+ B cells.
Cytogenetics: Conventional karyotype on the bone marrow aspirate:
46,add(X)(q22),Y,del(6)(q21),add(6)(q25),del(9)(q21q22),del(13)(q12q22),der(18)t(6;18)(p11.2;q21),+der(18)t(6;18)(p11.2;q21)[17]/46,XY[1]
FISH on the bone marrow aspirate:
Positive FISH study for 13q14.3 deletion in 40/200 cells (20%)
Molecular studies: No performed.
Proposed diagnosis: Intravascular large B-cell lymphoma
Interesting feature(s) of submitted case:
Clinical presentation with numerous unspecific CNS symptoms
Bone marrow involvement as diagnostic site
CD5 and MUM1 positivity consistent with typical immunophenotype of IVLBCL support this diagnosis
Complex karyotype

EAHP18-BMWS-340

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with t(14;19) and Complex Cytogenetics

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Case description: 88 year-old female presented with progressive shortness of breath, fatigue, night sweats and weight loss. On admission, her CBC showed hemoglobin 5.7 g/dL; platelets 25K/uL and WBC count of 260,000/uL. WBC differential count revealed absolute lymphocytosis (211,000/uL).
Pertinent Hematology/Oncology History:
Chronic lymphocytic leukemia (CLL) diagnosed in 2015. Diagnosis was confirmed by bone marrow biopsy. She was treated with Chlorambucil and had very good response. Her blood count normalized in a year since diagnosis until now.
Biopsy fixation details: Bone marrow biopsy and clot sections fixed using 10% neutral buffered formalin for 2 hours. Following fixation they are placed in filtered RDO rapid decalcifier (containing hydrochloric acid) for approximately 15 minutes. After decalcification, specimens are washed thoroughly for 30 minutes in running water after which they are loaded onto processors.
Frozen tissue available: No
Details of microscopic findings: Peripheral Blood Smear: Markedly increased atypical lymphocytes including small and mature lymphocytes with rounded nuclei, smooth nuclear contours, increased prolymphocytes and frequent medium and large lymphoid cells with markedly irregular nuclei were seen
Bone marrow, biopsy: Overall Cellularity: 98-100% with sheets of predominantly small, monotonous lymphocytes extensively infiltrating the entire marrow space. Scattered medium-to-large cells with single nucleoli are seen within the sheets of small lymphocytes. No sheets of large cells are observed.
Bone marrow aspirate: morphologic features similar to peripheral smear.
Immunophenotype: Flow cytometry (Peripheral blood and bone marrow aspirate):
Monoclonal B-lymphocytes represent 60% of all analyzed events with a composite antigen profile of CD19+, CD5+ (dim), CD23-/+, CD20+ (dim), CD200+, CD10 Neg., CD11c+ (partial, dim), CD3 Neg., CD38+ and kappa+
Bone marrow immunohistochemistry:
The lymphoid cells are positive for PAX5, CD5, and cyclin D1. CD23 is essentially negative, only rare positivity is noted. They are negative for CD3. MIB-1 nuclear proliferation rate is approx. 40-50%. No EBV positive cells are seen with in situ hybridization for EBV encoded mRNA (EBER).
Cytogenetics: Bone marrow karyotype:
47,XX,dup(1)(q23q42),der(12)t(3;12)(q21;q23),t(14;19)(q32;q13.3)[2]/47,XX,dup(1)(q23q42),t(2;14;19)(p12;q32;q13.3),der(12)add(12)(p12)t(3;12)(q21;q23)[10]/47,XX,dup(1)(q23q42),der(2)add(2)(p12)t(2;14;19)(p12;q32;q13.3),der(12)t(3;12)(q21;q23, add(13)(p11.2)[2]
Molecular studies: None
Proposed diagnosis: Atypical chronic lymphocytic leukemia/small lymphocytic lymphoma with t(14;19)(q32;q13.3)
Interesting feature(s) of submitted case: t(14;19) (q32;q13) seen in fewer than 0.1% of all B-cell neoplasms, juxtaposes the BCL3 gene at chromosome 19q13 with the immunoglobulin heavy chain (IgH) locus at chromosome 14q32. CLL with t(14;19) frequently shows atypical cytomorphology, atypical immunophenotype, complex cytogenetics and an aggressive clinical course.

EAHP18-BMWS-387

High grade B cell lymphoma, not otherwise specified (HGBL-NOS) with primary bone marrow presentation

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Case description: 71 year old woman presented with a month history of progressive lethargy, reduced appetite, night sweats and breathlessness. Complete blood count showed moderate neutropenia and thrombocytopenia accompanied by a leukoerythroblastic blood picture. There was no clinically palpable lymphadenopathy or hepatosplenomegaly. CTPA excluded pulmonary embolus or any alternative cause for respiratory symptoms. CT abdomen did not reveal any lymphadenopathy or splenic/hepatic enlargement
Biopsy fixation details: Paraffin embedded
Frozen tissue available: Not available
Details of microscopic findings: The bone marrow aspirate was a dry tap and trephine imprints showed dense infiltration by monomorphic population heavily vacuolated blast-like lymphoid cells. These are medium to large in size with oval nuclei, immature chromatin, and occasional 1-2 nucleoli. N:C ratio is high with modertaely basophilic cytoplasm. The majority of cells have cytoplasmic and/or nuclear vacuoles. Apoptotic cells and to lesser extent mitotic figures are encountered. The disease burden is >95%
Immunophenotype: Analysis of the lymphoid population shows population of B cells with reduced expression of CD19, CD45 and CD20 as well as absence of surface immunoglobulin. The cells are negative for the early antigens CD34 and TdT and positive for CD10. Ki-67 is markedly elevated at >90%. The immunophenotype is suggestive of high grade B cell lymphoma such as double hit or CD10+ diffuse large B cell lymphoma. It is not typical of Burkitt lymphoma.
Cytogenetics: Interphase Fluorescence In Situ Hybridisation studies revealed a signal pattern consistent with no MYC, BCL2 and BCL6 gene rearrangement in 99.6% 98.3%, 95.9% of 229, 231 and 221 nuclei examined respectively. Overall, the sample is negative for BCL-2, BCL-6 and c-myc gene rearrangement
Molecular studies: Not available
Proposed diagnosis: High grade B cell lymphoma not otherwise specified (HGBCL, NOS) with primary bone marrow presentation
Interesting feature(s) of submitted case: The presence of high grade B cell lymphoma primarily affecting the bone marrow without any accompanying lymphadenopathy or splenomegaly

EAHP18-BMWS-416

Triple hit follicle centre cell lymphoma with primary bone marrow and peripheral blood presentation

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Case description: A 78 year old male patient presented with gastrointestinal bleeding. He was found to be pancytopenic (Hb 91 g/L, WBC 1.2 x10*9 and platelets 20 x10*9, and had low serum fibrinogen and abnormal liver function tests. CT showed mild splenomegaly, a large splenic infarct and multiple small lymph nodes in pelvis with an enlarged prostate (suggestive of prostate cancer). There were no boney lytic lesions. Flow cytometry on the peripheral blood raised the possibility of Burkitt lymphoma. He was treated initially with intravenous methylprednisone, which improved performance status to allow for bone marrow sampling and treatment planning. Patient progressed (CNS involvement) after one cycle of R-DA-EPOCH and was put on palliative care.
Biopsy fixation details: 10% neutral buffered formalin, EDTA decalcification
Frozen tissue available: not available
Details of microscopic findings: The trephine biopsy samples a good length of hypercellular (~70%) bone marrow with a high volume (~80%) infiltrate of intermediate sized lymphoid cells. Most of these have a single prominent nucleolus, while a smaller population has three. The proliferation index (as determined by MIB-1 expression) is low (<10%) throughout the neoplastic population (stain repeated twice). Elements from all three cell lineages are present, but haemopoiesis is suppressed.
Immunophenotype: Immunohistochemistry performed on the trephine biopsy: The neoplastic cells express CD20 (variable), CD79a, CD10, BCL6, IRF4/MUM1 and C-MYC (>90%), but not CD3, CD5, CD23, Tdt, CD34, CYCLIN D1, CD138 or CD56. HHV8 and EBER-ISH are negative.
Immunocytochemistry/flow cytometry on peripheral blood: the neoplastic lymphoid cells express B cell lineage associated antigens CD19, variable CD20 (59%), CD22 (strong), CD79a and cytoplasmic IgM in addition to CD9, weak CD10, weak CD43, CD81 and strong HLA-DR. CD5, CD34, CD79b, CD200, TdT and surface light chains are not expressed.
Cytogenetics: no evidence of B-cell Acute Lymphoblastic Leukaemia (BCR/ABL1, ETV6/RUNX1, MLL rearrangements) related FISH abnormalities. Furthermore:
- 50% positive for the IGH-MYC t(8;14) rearrangement, with an aberrant signal pattern (2R2G1F2A).
- 33% positive for BCL6 (3q27) rearrangement with an atypical/variant breakpoint/signal pattern.
- The aspirate sample was negative for the IGH-BCL2 t(14;18) translocation. (FISH performed on the FFPE sample showed IGH-BCL2 translocation).
Molecular studies: Nothing additional.
Proposed diagnosis: Follicle centre cell lymphoma, ungradable, with MYC, BCL2 and BCL6 rearrangements.
Interesting feature(s) of submitted case: The difficulty in the classification of this neoplasm has arisen from the apparently conflicting high grade finding of MYC/BCL2/BCL6 rearrangements and the remarkably low proliferation index. As stated in the updated WHO classification, proliferation index is not a good predictor of underlying MYC/BCL2/BCL6-involved translocations in high grade B-cell lymphomas. Our case showed a particularly low proliferation index and consideration was given to the possibility of a 'triple hit' follicular lymphoma. Rare case reports have been published of de novo double hit follicular lymphomas with variable therapeutic responses and clinical outcomes.

EAHP18-BMWS-419

B cell leukemia with prolymphocytic features and MYC-IGH rearrangement, consistent with B-cell prolymphocytic leukemia (B-PLL)

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Case description: A 81 year-old man with no prior hematological history presented with elevated white count of 37 x 10^9/L with 86% of atypical lymphoid cells, splenomegaly (17 cm in largest dimension), diffuse lymphadenopathy (average SUV:5, highest SUV:11.5), fatigue and weight loss.
Biopsy fixation details: Bouin
Frozen tissue available: Yes
Details of microscopic findings: Bone marrow biopsy was hypercellular and largely replaced by a diffuse, monotonous proliferation of medium to large atypical lymphoid cells with round nuclei, moderately clumped chromatin, prominent central nucleoli and moderate amount of cytoplasm. There was limited residual maturing hematopoiesis. The bone marrow aspirate and peripheral blood smears showed atypical medium-sized cells with round to indented nuclei, moderately condensed chromatin, prominent central nucleoli and small amount of basophilic cytoplasm, consistent with prolymphocytes. Small atypical lymphocytes, including those with villous projections or with plasmacytoid differentiation, were not identified. A subsequent lymph node biopsy showed architectural effacement by a diffuse proliferation of atypical cells with similar morphologic features.
Immunophenotype: Flow cytometry on bone marrow aspirate and peripheral blood identified abnormal B cells which were CD45+ (bright), CD19+, CD20+ (bright), IgMl+ (moderately bright), CD5+ (dim), CD23+ (dim), FMC-7+ (dim partial) and CD7. CD10, CD103 and other T-cell antigens were not expressed. By immunohistology, neoplastic cells were positive for CD20, CD5 (weak), MYC, BCL2 and negative for CD3, cyclin D1, SOX11, DBA.44, CD25 and TRAP. The immunophenotype of the tumor cells in the lymph node biopsy was similar, except that CD5 and CD23 were negative, and no CD7 expression was observed.
Cytogenetics: A normal male karyotype was observed. FISH showed MYC-IGH rearrangement in 89% of nuclei analyzed. Three copies of BCL6 and four copies of BCL2 were also observed. A deletion of 13q14.3 region was present in 8% of nuclei screened. Trisomy 12, deletions of MYB, ATM and TP53 were not observed by FISH. CCND1(BCL1)-IGH was not detected.
Molecular studies: Next generation sequencing identified a clonal IGH rearrangement (V4-34*12 D3-16*01 JH*02), with a somatic hypermutation rate of 6.19%.
Proposed diagnosis: B cell leukemia with prolymphocytic features and MYC-IGH rearrangement, consistent with B-cell prolymphocytic leukemia (B-PLL).
Interesting feature(s) of submitted case: B-PLL is an extremely rare malignancy with aggressive course and chemotherapy refractoriness, affecting primarily bone marrow, peripheral blood and spleen. B-PLL needs to be distinguished from “prolymphocytoid transformation” of CLL or splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), and hairy cell leukemia (HCL) or variant with prolymphocytoid features. There is no clinical or morphologic evidence of preceding or concurrent CLL or SMZL in this case. In addition, the immunophenotypic profile is not typical for CLL (strong CD20 and light chain expressions) or SMZL (IgM+ only, IgD-, variable positivity for CD5 and CD23). The neoplastic B cells are negative for MCL and HCL-associated markers. FISH identified MYC-IGH rearrangement in addition to 13q14 deletion. MYC amplifications and gene rearrangements have been detected in a small cohort of B-PLL analyzed. 13q14 deletion has also been detected in PLL. Finally, most patients with B-PLL have absent or minimal lymphadenopathy. The extent of lymphadenopathy in our patient is not typical for B-PLL.

EAHP18-BMWS-441

Good clinical outcome in a patient with primary bone marrow high-grade B-cell lymphoma, not otherwise specified

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Case description:
A 69-year-old man with long standing history of mild thrombocytopenia was admitted to our hospital with pancytopenia. He complained of myalgias, fatigue, daily rigors, weight loss, headaches, and low grade fevers. Infectious disease work-up was negative. Imaging studies detected no lymphadenopathy or organomegaly. CBC revealed moderate to marked pancytopenia. Peripheral blood smear review showed 2% abnormal lymphoid cells. A bone marrow biopsy was performed.
Biopsy fixation details: Biopsy was placed in B5 fixative for 2 hours and decalcified prior to processing.
Frozen tissue available: No
Details of microscopic findings:
Cellular aspirate smears showed 60% abnormal lymphoid cells, characterized by a mixture of medium and large cells. The medium sized cells displayed finely textured chromatin, while large cells exhibited coarsely clumped chromatin and single prominent nucleoli with moderate amounts of dark blue cytoplasm. Cytoplasmic vacuoles were occasionally seen. Mitotic activity was high. Granulocytic and megakaryocytic hypoplasias were observed, though a mild erythroid hyperplasia was seen. Biopsy core demonstrated a hypercellular bone marrow with infiltrative lymphoma cells, distributed in a diffuse and interstitial pattern.
Immunophenotype:
Flow cytometry detected an abnormal population of intermediate to large sized B-cells with the following expression pattern: CD19, CD20 (bright), CD10 (dim), CD38 (dim), CD71 (partial), FMC-7 (bright), and HLA-DR. Surface immunoglobulin light chain expression was nonspecific in lymphoma cells, though a small population of small, polytypic B-cells was noted. The lymphoma cells were negative for CD5, CD23, and CD34. Immunohistochemical stains further revealed positivity of lymphoma cells for BCL6 and BCL2, and a high proliferation rate (90% of lymphoma cells positive). They were negative for MUM1, c-MYC, cyclin D1, and TdT.
Cytogenetics:
Chromosomal analysis was not obtained. FISH studies for MYC, BCL2, and BCL6 were performed. Results showed BCL6 rearrangement and additional copies of BCL2 and MYC, suggesting either gain of BCL2 and MYC or trisomy 18 and 8, respectively. No BCL2 or MYC rearrangements were detected.
Molecular studies: None
Proposed diagnosis:
High-grade B-cell lymphoma, not otherwise specified (HGBL-NOS), with primary bone marrow involvement.
Interesting feature(s) of submitted case:
HGBL-NOS (previously called “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma” in the 2008 WHO classification) represents a heterogeneous group of clinically aggressive mature B-cell lymphomas. Characterization of HGBL-NOS is incompletely defined as previous studies have reported them alongside other aggressive lymphomas (like double-hit lymphoma or double-expressor). Primary bone marrow presentation of non-Hodgkin lymphoma is rare and typically clinically aggressive. Our patient underwent 1 cycle of R-CHOP therapy followed by 6 cycles of R-EPOCH. He is currently in clinical and morphologic remission 4.5 years after initial disease presentation.

EAHP18-BMWS-442

Primary bone marrow presentation of diffuse large B-cell lymphoma with associated myelodysplastic hematopoiesis

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Case description: A 71 year old man was admitted in May 2013 after three weeks-history of weight loss, fever and night sweats. Physical examination was normal showing no enlarged lymph nodes or hepatosplenomegaly. The laboratory tests showed Hb 92 g/L, Platelets 80x10^9/L, WBC 5.64x10^9/L (lymphocytes 1.3x10^9/L), LDH 721 U/L (N=250-450). Bone marrow aspirate and biopsy were performed. In the light of the results, a PET-CT scan was carried out showing splenic FDG (Fluordesoxiglocose-F18) hypercaptation (SUV 3,6) and bone marrow diffuse FDG hypercaptation. The diagnosis of primary bone marrow diffuse large B-cell lymphoma with associated dysplastic hematopoiesis of unknown significance was established.
The patient received 6 cycles of chemotherapy (CHOP-R) achieving a complete remission. Since then the hemogram has remained normal, the bone marrow biopsy reveals no infiltration by lymphoma and the myelodysplastic features are borderline (10% in megakaryocytes and eythroblasts), with a normal karyotype. The patient has remained asymptomatic and disease-free more that 4 years after the initial diagnosis.
Biopsy fixation details: B13-019551 fixation with Bouin solution, decalcification with Decalcifier II Surgipath, B13-019552 fixation with formalin 10%, decalcification with formic acid 10%
Frozen tissue available: No
Details of microscopic findings: The bone marrow aspirate was hypercellular, with atypical large lymphoid cells of irregular distribution (5 to 40%). These cells had round or kidney-shaped nuclei with immature chromatin and abundant basophilic cytoplasm.
Erythroid precursors accounted for 37%, with 40% dyserythropoiesis; 31% granulocytic precursors were present with 80% dysgranulopoiesis; megakaryocytes were abundant, with 10% dysmegakaryopoiesis.
The bone marrow biopsy presented patched infiltration by atypical large cells with centroblastic morphology that amount to 20% of the total cellularity. In the non-infiltrated areas erythroid and granulocytic precursors were present with a normal M/E ratio, distribution and maturation. Megakaryocytes were slightly increased and there were few dysplastic elements.
Immunophenotype: Flow cytometry (aspirate) 0,8% B-cells with high FSC/SSC, CD45+, CD19+, CD20++, CD22++, CD79b+, CD10-, CD138-, CD38 dim.
Immunohistochemistry (biopsy): The atypical cells were CD20+, CD79a+, BCL2+, CD5+, MUM1+, CD10-, BCL6-, EBER-, Ki67 75%.
Cytogenetics: G-banded chromosomes obtained from 24-hour unstimulated bone marrow culture: 46, XY [20]
Molecular studies: Not performed
Proposed diagnosis: Primary bone marrow diffuse large B-cell lymphoma, NOS, of non-germinal centre subtype, with associated myelodysplastic hematopoiesis probably reactive.
Interesting feature(s) of submitted case: The clinical picture of a DLBCL with primary bone marrow presentation is rare (Chang et al, AnnHematol 2010, Martinez et al, Am J Surg Pathol 2012). They frequently manifest with fever of unknown origin, cytopenias, or elevated LDH and the reported outcome is poor; histologically most published cases correspond to DLBCL. Our case has a long follow up and is in complete remission more than four years after the initial diagnosis. The moderate PET-CT uptake of the spleen does not suggest a splenic origin of the DLBCL.
The associated morphological myelodysplastic changes in a patient with cytopenias raise the possibility of a concomitant myelodysplastic syndrome, but normal karyotype, no increase of blasts and disappearance after the lymphoma treatment support their reactive origin.

EAHP18-BMWS-448

CyclinD1 negative CD5 positive blastoid high grade B cell lymphoma

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Case description: 61-year-old female with a remote history of appendiceal adenocarcinoma s/p surgical resection, was in her usual state of health until she presented on 7/16/2017 with a severe headache and was found to have a large acute right sided subdural hematoma. Her PLT on presentation was 70. LDH level was elevated. CT scan on the same day revealed interval enlargement of the spleen to 16 cm from 2013, small bilateral pleural effusions and a 1cm hypodense nodule in the thyroid, otherwise unremarkable. A bone marrow biopsy was performed and the patient was subsequently started on 2 cycles of bendamustine + rituximab. The treatment was c/b acute kidney injury 2/2 tumor lysis syndrome, and acute anemia due to grade 3 splenic laceration requiring splenectomy. Pathologic evaluation of the spleen showed no evidence of involvement by a high grade B cell neoplasm.
Biopsy fixation details: Decalcified and subsequently fixed in formalin.
Frozen tissue available: N/A
Details of microscopic findings: Hypercellular biopsy and aspirate specimens show a diffuse lymphoid infiltrate of predominantly medium size cells with round to slightly irregular nuclei and fine chromatin taking up most of the cellularity (80-90%). Scattered larger lymphoid cells with prominent nucleoli are also present.
Immunophenotype: The infiltrate expresses CD20, CD5, CD10 (weak), SOX11, CMYC and BCL2 and is negative for BCL6, CyclinD1, EBER, CD30, and MUM1, CyclinD2, TdT. Ki-67~100%. P53 ~100%.
Flow cytometry: Monotypic B-cell population (49% of cells), positive for moderate kappa, dimmer CD19, CD20, partial FMC-7, CD5, partial CD10, CD38; negative CD23, TdT. The myeloid immunophenotypic findings show decreased granulocytes, normal myeloid and granularity, no increase in myeloid immaturity, and normal myeloid antigen maturation pattern.
Cytogenetics: Negative lymphoma panel for probes: BCL6, MYC/IGH, CCND1/IGH, and MYC breakapart.
Karyotype (peripheral blood): Abnormal female karyotype
46, X, -X, der(6)t(6;10)(q12;q11.2), add(8)(q24), del(9)(p?21), -10, del(12)(p11.2p13), del(13)(q14q22); del(17)(p11.2), idic(18)(p11.2), +idic(18)(p11.2)x2[cp7]/46, XX[13]
Molecular studies: N/A
Proposed diagnosis: High-grade B-cell lymphoma (HGBCL) with features suggestive of cyclinD1 negative blastoid mantle cell lymphoma (BMCL)
Interesting feature(s) of submitted case: CyclinD1 negative mantle cell lymphomas are characterized by high SOX11 expression, chromosomal rearrangements in CCND2, and a poor outcome with a 5 year OS of 48%. A subset of these, like classical mantle cell lymphoma can show blastoid morphology. BMCL can histologically and immunophenotypically resemble lymphoblastic lymphoma or simulate HBCL. CyclinD1 and CD5 co-expression and/or rearrangements of the CCND1 gene locus often distinguish between mantle cell lymphoma and other entities. Recently rare cases of B-cell lymphomas with features consistent with CyclinD1 negative BMCL have been reported. These cases morphologically and immunophenotypically overlap with CD5+ HGBCLs, and can only be distinguished either by gene expression profiling studies or SOX11 expression. Limited studies suggest that most cases of de novo CD5 positive DLBCL lack SOX 11 expression suggesting that SOX11 and CD5 positive aggressive lymphomas B-cell lymphomas may represent Cyclin D1 negative BMCL. This case shows cytologic features (medium sized cells with blastoid morphology), immunophenotypic features (CD20+, CD5+, CD10+, SOX11+) and genetic changes (complex karyotype) typical of BMCL but lacks Cyclin D1 expression or rearrangement. Therefore most likely represents cyclin D1 negative BMCL.

EAHP18-BMWS-453

A double-hit high grade B-cell lymphoma with a complex three-way translocation t(3;8;14)(q27;q24;q32) involving BCL6, MYC and IGH

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Case description: A 66 year old woman presented with dizziness and postural instability, left hypoacusis, generalized bleeding diathesis. Emergency exams revealed leukocytosis (WBC 18000) and thrombocytopenia (Plt 14000) with blasts in peripheral blood smear; CT scan identified subdural hemorrhage and meningeal thickening without mass effect and without any other visceral involvement or lymphadenopathy. Bone marrow aspirate and biopsy were performed in suspect of acute leukemia, probably lymphoblastic vs Burkitt lymphoma.
Biopsy fixation details: 10% buffered formalin and decalcification in EDTA.
Frozen tissue available: No.
Details of microscopic findings: Hypercellularity (90%) with complete replacement by diffuse, massive infiltrate of large monotonous cells with blastic appearence, scant cytoplasm, inconspicuous nucleoli and many mitotic figures (Fig.1-6).
Immunophenotype: Flow cytometry performed on bone marrow showed a lymphoid population with expression of CD19, CD20, CD22, CD38, CD45RA, CD43+/dim, cytCD79A. Immunistochemical stains performed on bone marrow biopsy showed CD20+, CD79a+, bcl6+, IRF4+, CD10-, bcl2+, TdT-, CD34-, CD30-.
Cytogenetics: Cytogenetics and FISH analysis were performed on bone marrow cultures with the following results: 47,XX,dup(1)(q25q32),+13,del(13)(q13q21)x2,add(14)(q3?1)[cp11]/46,XX[15]
.ish dup(1)(q25q32)(MEGF6+,ABL2++),t(3;8;14)(q27;q24;q32)(3'BCL6+,5'BCL6-,5'IgH+;5'MYC+,3'MYC-,5'BCL6+;3'IgH+,5'IgH-,3'MYC+),del(13)(q13q21)(D13S319-,LAMP1+)x2 (Fig.7)
FISH interphase nuclei analysis revealed gene rearrangements involving MYC (30%), BCL6 (24%) and IGH (20%), but not BCL2. FISH carried out on metaphases showed a complex three-way chromosome translocation t(3;8;14) involving BCL6, MYC and IGH genes (Fig.8-10).
FISH also confirmed the presence of a deletion on the long arm of two chromosomes 13 (17%) and a duplication of a part of the long arm of a chromosome 1 (17%) (data not shown).
Molecular studies: None.
Proposed diagnosis: Bone marrow localization of high grade B-cell lymphoma (non-GC type by Hans algorithm) with atypical double hit.
Interesting feature(s) of submitted case: In our case, both cytogenetics and FISH analysis showed a three-way chromosome translocation that involved MYC, BCL6 and IGH genes, showing similarities with the previously observed by Minakata et al. (Cancer Genetics, 2018). Both showed a three-way chromosome translocation but we observed MYC and BCL6 involvement instead of MYC and BCL2.
In conclusion, to our knowledge, this is the first reported double hit lymphoma with involvement of MYC and BCL6 by a three-way chromosome translocation.
FISH interphase nuclei analysis alone (break apart probes) could only suppose the presence of an atypical rearrangement, while by FISH on metaphases we had real evidence of a three-way chromosome translocation.

EAHP18-BMWS-460

High grade B cell lymphoma with rearrangement of MYC and BCL2 and/or BCL6, but with indolent clinical presentation and low grade cytology.

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Case description: 68 yo Vietnemese female presenting with thrombocytopenia and normocytic anemia. CT shows mild splenomegaly and minor retrocrural, retroperitoneal, and mesenteric adenopathy (2.5 cm maximum diameter). No prior history of lymphoma.
Biopsy fixation details: Formalin fixed paraffin embedded block.
Frozen tissue available: None
Details of microscopic findings: 90% diffuse involvement by CD10 positive B cell lymhoma with low grade cytology. Trilineage hypoplasia. Suboptimal smears (aparticulate). Blood smears with mild relative lymphocytosis, some larger atypical lymphocytes. CD20 dim pos/CD10 pos/bcl-2 pos/bcl-6 neg/c-myc dim pos (>40%)/Tdt neg/Ki-67 mod variable 50-60%
Immunophenotype: T-cells (23% of lymphoid cells) show a CD4/CD8 ratio about 3.6 without overt phenotypic abnormality. NKcells (2% of lymphoid cells) are unremarkable. A subset of mature B-cells (40% of lymphoid cells) are small in size based on the forward scatter pattern and show: CD5-, CD10+, CD11c-, CD19+, CD20+-, CD23-, CD38- with surface kappa light chain restriction (kappa:lambda 6.3). 30% of mature B cells are polytypic.
Cytogenetics: 46,XX[20]
Molecular studies: t(14;18): DETECTED BCL6 rearrangement: Not Detected
MYC rearrangement: DETECTED
MYC amplification: Not Detected
Fluorescence in situ hybridization (FISH) analysis was performed using probes specific for rearrangements involving BCL6, MYC, and
t(14;18), which are reported in high-grade/large B-cell lymphomas. This interphase FISH study revealed a break apart signal pattern
(1R1G1F, 20%, normal
BCL2) probe set.
This is an ABNORMAL result indicative of a MYC gene rearrangement, and t(14;18), which is evidence of a "DOUBLE/TRIPLE HIT"
lymphoma. The high risk "double/triple" hit lymphomas are characterized by a MYC translocation combined with a BCL6 and/or BCL2
translocation. In the appropriate morphologic setting, these FISH findings would suggest the WHO 2016 category High grade B-cell
lymphoma [HGBL], with rearrangements of MYC and BCL2 and/or BCL6.
t(14;18): DETECTEDBCL6 rearrangement: Not DetectedMYC rearrangement: DETECTEDMYC amplification: Not DetectedFluorescence in situ hybridization (FISH) analysis was performed using probes specific for rearrangements involving BCL6, MYC, andt(14;18), which are reported in high-grade/large B-cell lymphomas. This interphase FISH study revealed a break apart signal pattern(1R1G1F, 20%, normal
Proposed diagnosis: High grade B cell lymphoma with rearrangement of MYC and BCL-2 and/or BCL-6.
Interesting feature(s) of submitted case: Patient has low grade morphology, minor retroperitoneal adenopathy, some splenomegaly, and normal LDH and beta microglobulin. Suboptimal fixation (IHC results) and deceptive morphologic appearance.

EAHP18-BMWS-469

Pediatric Burkitt leukemia variant with t(8;14) and lack of surface and cytoplasmic immunoglobulin light chain expression

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Case description: The 7 year old female patient presents with a 2 weeks history of fever, abdominal pain, petechial rash on her neck, torso and ankles, joint and abdominal pain. The CT scan detected splenomegaly however, there was no lymphadenopathy except for a possible 1.3cm splenogastric nodule. Her CBC was remarkable for leukocytosis (WBC 41.4 x 109/L), thrombocytopenia (platelet count 33 x 10^9/L). Her LDH was >3,600 IU/L (reference range 100-220 IU/L) and her uric acid was 13.5 mg/dL (reference range 1.9-5.4 mg/dL). Her peripheral blood had 54% blasts and her bone marrow aspirate had 83.4% blasts.
Biopsy fixation details: The core biopsy was placed for 2 hours in B plus fixative, and submitted after a brief (<1 hour) decalcification to processing (formalin fixation for 2 hours and than is placed in the processor for embedding in parrafin in a Leika automatic tissue processor).
Frozen tissue available: No frozen tissue available.
Details of microscopic findings: Her peripheral blood is remarkable for 54% atypical medium to large size lymphoid cells, blast - like with round to irregular nuclei, with prominent one to multiple nucleoli, open to reticular chromatin, small amounts of dense basophilic cytoplasm and in a subset with fine intracytoplasmic vacuoles. The bone marrow is hypercellular for age and remarkable for extensive replacement of the normal hematopoiesis by a morphologically similar population of atypical nucleolated blast-like lymphoid cells, comprising 83.4% of a 500-cell count aspirate differential.
Immunophenotype: By flow cytometry immunophenotypic analysis performed on a peripheral blood sample were identified 50% large cells of B - cell lineage that express CD19 (bright), CD10, CD20, CD22, FMC7, CD38, CD9, CD24, HLA-DR and have bright CD45 positivity. These B-lymphoid cells are negative for CD34, TdT, surface and cytoplasmic immunoglobulin light chains, lack surface IgM and cytoplasmic mu, and are also negative for CD2, CD3, CD4, CD79b, CD58, CD25 CD117, CD13/CD33, CD14, CD64 and CD36. They are negative for myeloperoxidase cytochemical stain. By immunohistochemistry, the large PAX5+, CD10+ B-lymphoid population (approx. 80-90% of the nucleated bone marrow cells) is CD79a+ (weak) and MUM1+(weak), is variably c-myc+, has weak bcl2+ in a subset and has a proliferation rate of approximately 100% (MIB1 antibody). They are negative for CD20, CD34, CD31, CD30, bcl1, bcl6 and EBV-LMP, and have a weak blush - like cytoplasmic staining with CD43. There are very few scattered TdT+ nuclei seen (? residual hematogones), however the large majority of the PAX5+ B-lymphoid cells are negative for TdT expression.
Cytogenetics: Karyotype is 46,XX,+1,dic(1;22)(p32;p11.2),dup(1)(q21q44),t(8;14)(q24;q32)[4]/46,XX[16].
FISH: Positive for MYC rearrangement.
Molecular studies: Negative of IGH/bcl2 and BCR/ABL1 fusion transcript.
Positive for IGH rearrangement.
Proposed diagnosis: Pediatric Burkitt leukemia variant with t(8;14) and lack of surface and cytoplasmic immunoglobulin light chain expression.
Interesting feature(s) of submitted case: This case is remarkable for its unusual presentation with virtual absence of lymphadenopathy. This pediatric Burkitt leukemia variant with t(8;14) is associated with an aberrant immunophenotype, indicative of a more immature B-lymphoid population due to lack of surface and cytoplasmic immunoglobulin light chain expression and by immunohistochemistry lack of CD20 and bcl6 positivity. Of interest, the WHO 2016 classification authors recognize that approximately 2% of otherwise classic pediatric Burkitt leukemias with a t(8;14) (q24;q32) or variant MYC translocation have an aberrant phenotype of precursor B-cells.

EAHP18-BMWS-475

A young woman with bone marrow involvement by B-cell lymphoma

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Case description: A 36-year-old woman presented with severe symptomatic anemia (HGB 4.5 g/dL) following an uncomplicated cesarean section. On initial work-up, there was no evidence of bleeding, hemolytic anemia, or nutritional deficiency. A CT scan identified moderate splenomegaly, but no lymphadenopathy. The patient required several transfusions over the course of 2 weeks, without improvement in the anemia, prompting a bone marrow biopsy. CBC results concurrent with bone marrow biopsy: WBC 9.3 x 10^9/L; HGB 6.4 g/dL; HCT 19.0%; MCV 89.6 fL; PLT 107 x 10^9/L. Manual differential: 26% polys; 67% lymphs; 6% monos; 1% eos.
Biopsy fixation details: Formalin-fixed, decalcified, paraffin-embedded tissue sections
Frozen tissue available: None
Details of microscopic findings: The marrow cellularity is overall approximately 85%. The myeloid to erythroid ratio is markedly increased, and erythroid maturation is complete, but scarce. There are multiple small and large non-paratrabecular lymphoid aggregates comprised of small lymphoid cells with irregular nuclei and moderately abundant pale cytoplasm, accounting for 40% of the marrow cellularity.
The bone marrow aspirate shows 45% neutrophils and precursors; 3% erythroid precursors; 47% lymphocytes; 1% monocytes; 2% promyelocytes; 1% blasts; and 1% plasma cells. The lymphocytes are small-to-medium-sized with scant to moderately abundant, pale cytoplasm.
On the peripheral smear reveals, the lymphoid cells have pale blue cytoplasm with generally smooth surface borders and slightly irregular nuclei.
Immunophenotype: Immunohistochemistry shows that the lymphoid aggregates consist predominantly of CD20+, BCL2+, CD5+, LEF1+, CD10-, cyclinD1-, SOX11- B-cells. BCL6 shows non-specific staining of myeloid elements and is weakly positive in some lymphoid cells. Ki67 shows a low proliferation index of 5% in the lymphoid cells.
Flow cytometry on the marrow revealed a monotypic CD19+, CD20+, CD5 (dim), CD10-, CD23-, CD200+, CD38- lambda light chain-restricted B-cell population. Flow cytometry on the blood showed 0.4 x 10^9/L monotypic B cells with a similar immunophenotype to the blood, in a background of polytypic B cells.
Cytogenetics: Peripheral blood cytogenetics (with CpG stimulation): 46,XX,t(5;5)(q11.2;q35)[5]/47-48,idem,+12[2],+21[3][cp5]/46,XX[10]. FISH is negative for t(11;14) CCND1-IGH gene rearrangement.
Molecular studies: Molecular genetic testing (PCR) on blood was negative for MYD88 mutation.
Proposed diagnosis: Low-grade B-cell lymphoma (small lymphocytic lymphoma vs. splenic marginal zone lymphoma)
Interesting feature(s) of submitted case: The overall constellation of findings (particularly CD5, CD200, and LEF1 positivity) and bone marrow infiltration pattern tend to favor a diagnosis of small lymphocytic lymphoma. However, the patient's presentation with isolated splenomegaly without lymphadenopathy or significant circulating disease, CD23 negativity and relatively bright CD20 expression seen by flow cytometry are unusual and raise the differential diagnosis of a CD5+ splenic marginal zone lymphoma. The cytogenetic findings are not specific for either entity and thus definitive distinction between these two possibilities cannot be made. Of note, there is marked erythroid hypoplasia, which in the setting of severe anemia (that is not accounted for by the degree of bone marrow lymphomatous involvement) likely represents a paraneoplastic pure red cell aplasia, which can occur both with SLL/CLL and with other B-cell lymphomas.

EAHP18-BMWS-481

Primary bone marrow diffuse large B-cell lymphoma with non-germinal center cell related phenotype

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Case description: 75 years old male with chronic obstructive pulmonary disease and history of few weeks of fever and malaise with no improvement on antibiotics. CT showed no lymphadenopathy and no hepatosplenomegaly. Laboratory data: Hb 85g/L , WBC 5,4x10^9/L, normal differential count, Plt 96x10^9/L, Retic 194 x10^9/L, DAT negative haemolysis, LDH increased, increased ferritin and triglycerides. The patient's blood status did not improve on steroids. Rituximab was given but the patient had anaphylactic shock and treatment was discontinued. Due to worsening thrombocytopenia 35x10^9/L another bone marrow biopsy was taken 6 weeks after the first one. Unfortunately the patient died 2 months after primary diagnosis.
Biopsy fixation details: Bone marrow biopsies get fixed in 4% buffered formaldehyde for 1h and then processed in the LOGOS J hybrid tissue processor (Milestone, Bergamo, Italy), that uses 10% formaldehyde for fixation and ethylene diamine tetra acetate 10% (EDTA) for decalcification.
Frozen tissue available: No
Details of microscopic findings: Two biopsies are submitted (16PL07819 and 16PL12561 taken 6 weeks later). The first one shows variable cellularity including hypercellular areas with increased granulopoiesis and erythropoiesis. No large infiltrates are seen but CD20 staining detects groups of large CD20+ cells. The second biopsy shows extensive fibrotic infiltrates with morphology consistent with diffuse large B-cell lymphoma.
Immunophenotype: At the first time point, flow cytometry showed 2.4% B-cells with kappa/lambda ratio 5.2 suggesting clonal excess of kappa. At the second time point B-cells were 4% and all positive for kappa. Immunohistochemistry showed CD20+, CD79+, BCL6+, MUM-1+, BCL-2+, Ki67+>90%.
Cytogenetics: Not done
Molecular studies: Not done
Proposed diagnosis: Primary bone marrow diffuse large B-cell lymphoma
Interesting feature(s) of submitted case: This case fulfills criteria for Primary Bone Marrow Lymphoma: isolated bone marrow infiltration with no evidence of nodal or extranodal involvement. Only rare cases are described and diffuse large B-cell lymphomas (DLBCL) is the most common. In this case the first biopsy showed minimal involvement, not easily seen by morphology but suggested by clonal excess of kappa+ B-cells at flow cytometry and CD20 immunohistochemistry on BM biopsy.

EAHP18-BMWS-498

Richter's transformation with TP53 mutations in a patient with history of chronic lymphocytic leukemia, following a diagnosis of therapy related-myelodysplastic syndrome with excess blasts.

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Case description: A 72-year-old man presented in late 2011 with WBC>600,000/uL, anemia, dyspnea and cervical lymphadenopathy. He was diagnosed with chronic lymphocytic leukemia (CLL) with marrow involvement (06/2012) and received 6 cycles of fludarabine and rituximab. He developed persistent thrombocytopenia only partially improved by romiplostim. In 06/2014, CLL showed signs of progression but was controlled with ibrutinib. In 12/2016, anemia developed (hemoglobin: 8.5 g/dL) and a bone marrow biopsy (BMB, 01/2017) showed myelodysplastic syndrome with excess blasts-2 (MDS-EB2) and minimally persistent CLL. Decitabine was started. In 04/2017, he developed flank pain, increasing leukocytosis and a renal mass was found. Marrow and kidney biopsies showed a Richter's transformation to diffuse large B-cell lymphoma. The patient died a few weeks later of rapidly progressive disease.
Biopsy fixation details: BMBs were fixed in B+ fixative and decalcified with Rapid Cal solution. The kidney biopsy was formalin-fixed and paraffin-embedded.
Frozen tissue available: No.
Details of microscopic findings: BMB, 06/2012: Cellularity 50% with left shift of myeloid and erythroid lineages and no dysplasia. Scattered non-paratrabecular aggregates of small lymphocytes with round to irregular nuclei accounting for 20% of cells.
BMB, 01/2017: Cellularity 40%, with marked dysplasia in all lineages and increased megakaryocytes, including small forms and micromegakaryocytes. Blasts are increased (10%) and occur in clusters. Scattered aggregates of small lymphocytes account for 5% of cells.
BMB, 04/2017: Cellularity 90%, with almost complete replacement by sheets of large lymphoid cells with round to irregular nuclei, vesicular chromatin, prominent nucleoli and scant cytoplasm (95% of cellularity). Foci of geographic tumor cell necrosis present.
Immunophenotype: BMB, 06/2012. Flow cytometry: B cells (CD19+/CD20-/CD5+/CD10-/CD23+) with monotypic dim surface kappa immunoglobulin light chain expression.
BMB, 01/2017. Myeloid blasts and a subset of megakaryocytes are CD34+. p53 is strongly positive in 15% of the hematopoietic cells and in many of the lymphoid cells. B cells in the lymphoid aggregates are PAX5+/LEF1+. Flow cytometry: 1% clonal B cells (CD19+/CD20dim/CD5+/CD10-/CD23dim) with monotypic kappa light chain expression.
BMB, 04/2017. Large lymphoid cells express PAX5/CD20/CD79a/CD5/LEF1/p53/c-MYC/CD19 (partial) and no CD3/CD34/CD117/TdT. No CD34+ blasts are seen. Flow cytometry: non-contributory.
Cytogenetics: Blood 01/2017: complex karyotype (see PowerPoint).
Blood 04/2017: complex karyotype (see PowerPoint); FISH shows a MYC gene rearrangement.
Molecular studies: Blood 01/2017: SNAPSHOT-NGS Assay (54 genes): TP53 p.Arg273His (VAF: 41%,); TP53 p.Val173Leu (VAF: 16%).
Blood 04/2017: SNAPSHOT-NGS Assay (54 genes): TP53 p.Arg273His (VAF: 7%,); TP53 p.Val173Leu (VAF: 73%).
Proposed diagnosis: Diffuse large B cell lymphoma consistent with Richter's transformation in a patient with history of CLL, following a diagnosis of therapy related-MDS-EB2.
Interesting feature(s) of submitted case: SNAPSHOT study showed two distinct TP53 mutations which differed in frequency in the t-MDS and Richter's samples. A p53 stain was strongly positive in both. These findings suggest the presence of two distinct TP53 mutations, one in the MDS clone and one in the Richter's/CLL clone. A MYC rearrangement was confirmed by FISH in the Richter's, and together with the TP53 mutations, this likely contributed to the transformation of the CLL. Of note, only 3 months prior to the Richter's transformation, the CLL involvement of marrow was minimal and the marrow picture was dominated by the t-MDS-EB.

EAHP18-BMWS-499

Unusual Initial Presentation of T-cell/histiocyte-rich Large B-cell Lymphoma in the Marrow of a 17-year-old Immunocompetent Boy

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Case description: Our patient is a 17-year-old boy who presented with intermittent right upper quadrant pain for two weeks, fever with chills and night sweats for one week. Laboratory investigation demonstrated leukopenia (WBC 2.2 K/µL) with an absolute neutropenia (neutrophils 0.9K/µL), normocytic anemia (Hb 10 g/dL), and thrombocytopenia (platelet count 93 K/µL). Radiology revealed hepatosplenomegaly with hyperechoic lesions in the spleen.
Biopsy fixation details: After decalcification, the bone marrow core biopsy was fixed in neutral buffered formalin and embedded in paraffin.
Frozen tissue available: No
Details of microscopic findings: The bone marrow aspirate smears showed trilineage hematopoiesis with orderly maturation and a few lymphohistiocytic aggregates. The core biopsy showed a dense lymphoid infiltrate (comprised mostly small, mature lymphocytes with few admixed histiocytes and few large atypical lymphoid cells), occupying 40% of the marrow space. The uninvolved areas showed unremarkable bone marrow.
Immunophenotype: Flow cytometry evaluation on the bone marrow aspirate was unremarkable. Immunostains on core biopsy showed that the small lymphocytes were CD3/CD5/CD7 positive unremarkable T-cells showing a mixture of CD4 and CD8 positive cells. CD20 and PAX-5 identified very rare positive staining atypical cells. TdT, ALK-1, CD56, EBER were negative. CD30 identified very rare positive cells. Ki-67 was positive in large atypical cells.
Cytogenetics: 46,XY[20].
Molecular studies: N/A
Proposed diagnosis: T-cell/histiocyte rich large B-cell lymphoma
Interesting feature(s) of submitted case: Given the patient's age and bone marrow findings, we entertained the possibility of T-cell/histiocyte rich large B-cell lymphoma. A nodular lymphocyte predominant Hodgkin lymphoma is always another differential diagnostic possibility and in smaller needle/core biopsies it may not be possible to distinguish between the two entities. While marrow fibrosis and dense infiltration could be a feature of classic Hodgkin disease, we did not favor this due to the absence of history of immunosuppression and the phenotype of the large cells. Given the dense nature of the T-cell infiltrate seen in our case, a T-cell lymphoma was also initially thought of and ruled out based on the unremarkable morphology and immunophenotype of the T-cell compartment. Furthermore, a T-lymphoblastic leukemia/lymphoma was also excluded.
Although it was very difficult to make a definitive subclassification of the lymphoma in the bone marrow biopsy, presence of very very few small B-cells in the lymphoid infiltrate and the morphology of large atypical neoplastic cells indicated that a nodular lymphocyte predominant Hodgkin lymphoma was less likely and we favored the diagnosis of T-cell/histiocyte rich large B-cell lymphoma, however, we recommended a tissue biopsy for confirmation. Subsequently the patient underwent a lymph node biopsy which confirmed the diagnosis of T-cell/histiocyte-rich large B-cell lymphoma.
This case underscores the challenge in a primary definitive diagnosis of a T-cell/histiocyte-rich large B-cell lymphoma in small biopsies, especially a bone marrow core biopsy. T-cell/histiocyte-rich large B-cell lymphoma is generally a disease of middle-aged men and is somewhat under recognized. The difficulty in diagnosis is compounded by it's rarity in the pediatric population because and more so on a small biopsy which lacks architectural features.
The authors wish to thank Dr. Stefania Pittaluga and Dr. Elaine Jaffe of National Institutes of Health/National Cancer Institute, Bethesda, MD, USA for their help with the diagnostic evaluation of this case.

EAHP18-BMWS-515

EPSTEIN BARR VIRUS POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA

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Case description: A 61 years old female, with a medical history of poliomyelitis and hepatitis A, presented with painful unilateral cervical lymphadenopathy evolving for 3 months.
Peripheral blood findings showed anemia (10,8 g/dl), with normal leucocyte and platelet counts.
The patient underwent cervical and thoracic CT scan which revealed an inferior left latero-cervical mass, extended to supraclavicular and infraclavicular regions, measuring 5.7x 4.4 x 2.3 cm with compression of the left thyroidlobe. Ultrasonography showed multiple subdiaphragmatic lymphadenopathies located as follows: hepatic hilum (measuring 21 x 12 mm), celiac trunk (measuring 27 x 17 mm), inframesenteric (measuring 12 x 10 mm), lumbar-aortic (measuring 17 x 7.6 mm).
Biopsy fixation details: 10% buffered formaldehyde fixation; Na2 EDTA decalcification
Frozen tissue available: Not available
Details of microscopic findings: Histopathological examination of BMB revealed diffuse polymorphous infiltrate rich in small lymphocytes and histiocytes. In this reactive background, numerous atypical large lymphocytes, scattered and in clusters were seen. They showed vesicular nuclei with, 1-3 conspicuous nucleoli. One of the cells shozed Hodgkin/Reed-Sternberg-like morphology. Secondary fibrosis (grade 1) was observed very restricted areas revealed preserved hematopoiesis.
Immunophenotype: The tumor cells were large malignant B lymphocytes, uniformely and strongly positive for CD20 and PAX5. They also expressed CD79a (isolated cells), CD30, BCL2, CD45 (isolated cells). In addition they were EBV/LMP1 positive and showed a no-germinal center phenotype (non-GC), with expression of MUM-1/IRF4 and negativity for CD10 and BCL6. They were negative for CD15. The small reactive lymphoid cells were T cells, CD3 positive.
Cytogenetics: Not performed on this case
Molecular studies: Not performed on this case
Proposed diagnosis: The histopathological and immunohistochemical findings are consistent with the diagnosis of EBV-positive diffuse large B-cell lymphoma, not otherwise specified
Interesting feature(s) of submitted case: Some overlopping with a classic Hodgkin's lymphoma

EAHP18-BMWS-522

ALK-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA

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Case description: A 64 years old male patient was admitted to our department in May 2012 with altered general state and B symptoms (fever and weight loss). Clinical examination revealed multiple superficial laterocervical, axillary and inguinal lymphadenopathy.
Peripheral blood findings showed anemia (8,5 g/dl), thrombocytopenia (63.000/mm3) and leucopenia (3200/mm3).
The patient underwent thoracic and abdominal CT scan which revealed hepatosplenomegaly and multiple abodominal lymphadenopathy (para-aortic and mesenteric), measuring between 1,5 and 2 cm in diameter.
After the diagnosis was made, he was submitted to 1 cycle of chemotherapy regimen with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and we lost the follow-up of the patient after the initiation of therapy.
Biopsy fixation details: 10% buffered formaldehyde fixation, Na2EDTA decalcification
Frozen tissue available: not available
Details of microscopic findings: Histopathological examination of the bone marrow biopsy revealead a diffuse neoplastic infiltrate composed of monomorphic large cells, with round, centrally located nuclei, prominent nucleolus and slight basophilic cytoplasm; scattered hematopoietic cells are randomly distributed throughout the neoplastic cells.
Immunophenotype: Immunohistochemical assessment of the bone marrow biopsy disclosed the large malignant cells to express CD45, EMA, CD138, show light chain restriction (kappa/lambda ratio 1:20), IgA and ALK1 (cytoplasmic stainig). Neoplastic infiltrate was negative for CD20, CD43, CD30, AE1/AE3 and S100 protein.
Cytogenetics: not performed
Molecular studies: not performed
Proposed diagnosis: The histopathological and immunohistochemical findings are consistent with the diagnosis of ALK-positive large B-cell lymphoma.
Interesting feature(s) of submitted case: ALK-positive large B-cell lymphoma is a rare pathological entity (accounting for < 1% of DLBCL) and the bone marrow involvement is even more rarely encountered. Due to plasmablastic morphology and positivity for plasmacytic differentiation markers like CD138, recognition of this entity can prove challenging to distinguish from a plasmablastic lymphoma or plasmablastic myeloma. Differential diagnosis of ALK+ DLBCL should also include ALK+ ALCL (due to morphological appearance and presence of ALK-positive staining), but CD30 was negative and the malignant cells were lambda IgA positive.

EAHP18-BMWS-536

Diffuse large B-cell lymphoma with primary bone marrow presentation

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Case description: The patient was 69 year old female with a 3 month history of fever of unknown origin and altered mental status. The patient was known to have atrial fibrillation with pacemaker placement, and recently developed pancytopenia requiring RBC transfusions. Due to clinical suspicion of myelodysplastic syndrome, bone marrow exam was performed.
Biopsy fixation details: Formalin fixed, nitric acid decalcified
Frozen tissue available: No
Details of microscopic findings: Bone marrow was hypercellular (80%) with increased erythropoiesis and granulopoiesis, and adequate megakaryopoiesis. Large atypical cells with pleomorphic nuclei with prominent nucleoli and abundant cytoplasm were seen predominantly in a sinusoidal pattern.
Immunophenotype: Immunohistochemical stains: Large atypical cells were positive for CD20, PAX5, MUM1 and CD5, and negative for BCL6, CD30, cyclin D1 and CD138.
Flow cytometry: Monoclonal population of B-cells positive for CD20, CD19, CD5 and kappa light chain, and negative for CD10.
Cytogenetics: Twenty dividing cells were analyzed and nine cells showed a composite near tetraploid clone with a modal number between 86 and 92 chromosomes and numerous structural abnormalities.
MDS FISH: positive for 4 copies of chromosomes 5, 7q, 8 centromere and 20q; 5 copies of 8 centromere; positive for 5 copies of MLL; negative for MLL gene rearrangement.
Molecular studies: Not performed
Proposed diagnosis: Bone marrow involvement by diffuse large B-cell lymphoma, NOS.
Interesting feature(s) of submitted case: The bone marrow showed morphologically subtle, diffuse involvement with predominantly but not exclusively intrasinusoidal pattern. Diagnosis was facilitated by immunohistochemistry and flow cytometry. The patient died shortly after diagnosis. Diffuse involvement of periaortic and abdominal lymph nodes, spleen, liver and lungs were seen on the autopsy. Similar cases have been reported previously and typically presented with cytopenias. Reported cases showed similar post-germinal center immunophenotype with frequent coexpression of CD5 antigen. The clinical course was aggressive with a median survival of less than 6 months.

EAHP18-BMWS-537

A young woman with splenic T-cell / histiocyte-rich large B-cell lymphoma presenting as pancytopenia

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Case description: A 41 year-old woman presented with signs of progressive pancytopenia. No signes of dysplasia, no blasts. A bone marrow biopsy was performed, an aspirate was a dry tap. The bone marrow biopsy revealed a T-cell and histiocyte-rich inflammatory infiltrate with scattered large, atypical B-cells. Scattered EBV-positive B-cells were seen. Molecular tests were inconclusive (pre-analytical DNA degradation). Serology prevealed a non-healed Hepatitis B infection and status post-EBV infection. A HIV test was negative. The patient was not immunosuppressed and had been healthy previously, apart from a vague history of back pain with unclear foci of bone marrow enhancement, with negative biopsy rresults ca. 2 years prior. The PET-CT revealed no lymphadenopathy, PET-avid lesion in hepatic segment VII, moderate splenomegaly and diffuse positivity in the bone marrow. An additional bone marrow biopsy was performed. The aspirate was almost a dry tap. Few atypical B-cells were isolated land ambda light chain restricted Extensive work-up of the bone marrow, (incl. molecular pathology, FISH) was still inconclusive. Because of worsening clinical presentation and increasing splenomegaly a diagnostic splenectomy was performed. The spleen (470g) revealed multiple white nodules up to 0,9cm in diameter. The morphological and immunohistochemical presentation suggested an aggressive B-cell lymphoma, compatible with T-cell / histiocyte-rich large B-cell lymphoma. The patient is currently undergoing R-CHOP chemotherapy, planned to be followed up by high dosis consolidation.
Biopsy fixation details: 10% neutral buffered formalin
Frozen tissue available: Bone marrow: no. Spleen: yes
Details of microscopic findings: Bone marrow: Packed marrow, normal hematopoiesis subtotally replaced by dense infiltrate of mature T-cells and histiocytes/ granulomas. Focally prominent eosinophils,f ew plasma cells, moderately abundant B-cells. Scattered large, atypical B-cells with hyperchromatic, in part polylobulated nuclei +/- prominent nucleoli. No typical HRS morphology. Special stains (PAS, Giemsa, Ziel-Nelson): microorganisms. MF-1 myelofibrosis.
Spleen: 470g diffuse white nodules 0,3cm and 0,9cm. Within these nodules T-cell and histiocyte-rich areas, without obvious granulomas. Very few eosinophils and scattered, ipartly group edlarge, atypical B-cells with identical morhplogy as in the bone marrow. No FDC networks. Perifocally normal white and red pulp architecture.
Immunophenotype: Atypical / neoplastic B-cells: Expression of CD20, Pax-5, CD79a, MUM-1, Oct-3, BBOB-1, weak Bcl-6, bcl-2, CD30, LCA. Light chain restriction lambda. Negativity for CD10, CD15, J-Chain, EMA, ALK and all T-cell markers (CD3, CD4, CD5, CD7, CD8, TIA-1 and Granzyme B). o PD-1 positive T-cell rosettes and no FDC networks (CD23, CD21)
Bone marrow: scattered EBER positive cells, latency type 1 (EBNA2 and LMP1 negative).
Cytogenetics: Bone marrow biopsy: FISH negative for t(11;14) or t(14;18). Spleen: Not performed.
Molecular studies: Bone marrow: Multiplex PCR for IgH and TCRg gene rearrangement. IgH not conclusive (too low DNA content), polyclonal TCRg. Spleen: Not performed.
Proposed diagnosis: Aggressive B-cell non-Hodgkin lymphoma, favour T-cell / histiocyte-rich large B-cell lymphoma
Interesting feature(s) of submitted case: 1) Clinical presentation with progressive pancytopenia - complete and diffuse bone marrow involvement. 2) extensive histiocytic / granulomatous reaction in the bone marrow masking lymphoma - DD of non-neoplastic inflammatory infiltrate in reaction to granulomas
3) Relevance (?) of few EBV-positive cells in bone marrow biopsy no longer present in splenectomy

EAHP18-BMWS-538

Aggressive B-cell lymphoma presenting as an acute leukemia

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Case description: The patient is a 68-year-old male with a history of esophageal and non-small cell lung cancer treated with radiation and chemotherapy in 2016.. He presented to his oncologist with complaints of weakness, fatigue, weight loss and night sweats. Blood work revealed anemia, thrombocytopenia, and reported blasts. A bone marrow aspiration and biopsy were performed to rule out an acute leukemia. Peripheral blood values (reference ranges): WBC 8.5x109/L (3.8-10.6),Hemoglobin 12.4 g/dl(12.9-16.9), Hematocrit 36.2% (38.0-48.8), MCV 90.7 fl (82.6-97.4),Platelets 22x10^9/L (156-369). Differential: Polys 28%, Bands 19%, Lymphocytes 14%, Monocytes 19%, Eosinophils 4%, Basophils 2%, Blasts 10%, Promyelocytes 1%, Metamyelocytes 3%, 9 NRBCs/100 WBCs. Bone marrow aspirate smears were aspicular. 400 cell count differential on the touch imprint demonstrated 62% Blasts/Atypical cells, 1.5% Myelocytes/Metamyelocytes, 13% Bands, 5.8% monocytes, 13% lymphocytes, 0.8% Eosinophils, 0.5% Basophils, 3.5% Normoblasts.CT scans did not demonstrate lymphadenopathy or hepatosplenomegaly.
Biopsy fixation details: B+
Frozen tissue available: No
Details of microscopic findings: Cells classified as blasts in the peripheral blood (Wright-Giemsa) (Images 1-6) demonstrated variable but mostly large size, mostly rounded nuclear contours, basophilic often vacuolated cytoplasm, condensed nuclear chromatin and variably prominent nucleoli. The touch imprint (Wright-Giemsa) demonstrated similar cells (Image 7) with rare hematopoietic cells. The marrow biopsy (H&E) (Images 8) was hypercellular for age (60-70%) with an extensive infiltrate of mononuclear cells with prominent nucleoli (Image 9). By immunohistochemistry,the mononuclear cells were CD20 positive (Image 10), MYC positive (Image 11), bcl-2 negative (Image 12) and bcl-6 variably positive (Image 13). Ki-67 (Image 14) indicated >50% positive cells, IRF4/MUM1 appeared negative to weakly positive (Image 15)). Cyclin D1, Tdt, CD30, CD34, and EBV-ISH immunohistochemical stains were negative.
Immunophenotype: Flow cytometry studies performed on the bone marrow demonstrated kappa monotypic, CD19 positive, CD20 positive, CD5 negative, CD10 positive, BCL-2 indeterminate, CD34 negative, Tdt negative B-cells. Few T-cells, 3% CD34 positive cells, few monocytes, few basophils and few granulocytes were present.
Cytogenetics: 45~46,XY,der(3;?)(q10;?),add(4)(q31),t(8;14)(q24.1;q32),-9,-11,der(14)t(8;14)(q24.1;q32)t(14;?)(p11.2;?), 17,add(17)(p11.2),+mar1,+mar2[cp15]/46,XY[5]:. Fluorescence in situ hybridization (FISH) was positive for the MYC (14.1%), IGH (13.6%) and IGH/MYC (16.4%) gene rearrangements and negative for BCL6 and BCL2 gene rearrangements.
Molecular studies: BCR/ABL1 Major (p210), BCR/ABL1 Minor (p190) transcripts, PML/RARA intron 3 and Intron 6 breakpoint transcripts were not detected by quantitative real-time PCR.
Proposed diagnosis: High grade B-cell lymphoma, NOS
Interesting feature(s) of submitted case: Interesting features of the case: The iperipheral blood findings of 10% apparent "blasts" suggested the possibility of an acute leukemia or a blastoid variant of mantle cell lymphoma. Flow cytometry studies and immunohistochemical stains supported the presence of a mature B-cell lymphoma. While the morphologic and clinical features suggested a double-hit lymphoma, BCL2 and BCL6 gene rearrangements were not identified by FISH, although some bcl-6 positivity was seen with immunohistochemistry. DA-EPOCH and rasburicase for tumor lysis syndrome were initiated, but the patient expired from respiratory distress and refractory lactic acidosis shortly after diagnosis.

EAHP18-BMWS-542

An aggressive case of primary bone marrow B-cell non-Hodgkin lymphoma

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Case description: A 78-year-old Vietnamese man presented to UC Irvine Medical Center with a one-week history of anorexia and generalized weakness. His past medical history was significant for metastatic papillary thyroid cancer, treated with radioactive iodine ablation, thyroidectomy, and axitinib.
His physical exam at presentation was unremarkable. CT-imaging demonstrated interval increase in splenic and hepatic size, but no concerning masses or lymph nodes. However, the patient's admission LDH was 4866 U/L and his WBC count was 454 x 10^3/µL. His peripheral blood smear was notable for innumerable large lymphocytes, and subsequent bone marrow biopsy revealed CD5-positive diffuse large B-cell lymphoma involving 70-80% of a hypercellular marrow. The patient received six cycles of EPOCH-R. Repeat bone marrow biopsy following cycle 2 demonstrated a normocellular marrow with no lymphoma involvement, and follow-up imaging confirmed a complete response. Five months later, the patient developed biopsy-confirmed relapse in right inguinal lymph nodes. Currently, the patient is receiving gemcitabine/oxaliplatin. His most recent bone marrow demonstrates no lymphoma involvement.
Biopsy fixation details: Bone marrow cores and clot were initially fixed in 10% neutral buffered formalin, then immersed in decalcifying solution for 30 min.
Frozen tissue available: Not available
Details of microscopic findings: The patient's peripheral blood contained innumerable medium- to large-size lymphoma cells. No circulating blasts were seen. The bone marrow aspirate smear included sheets of similar-appearing cells, featuring blastic morphology with scant cytoplasm, irregular nuclear contours, and prominent nucleoli. The bone marrow core was hypercellular with lymphoma cells constituting 70-80% of the total marrow cellular element. Numerous apoptotic bodies and mitotic figures were identified.
Immunophenotype: Flow cytometry of the lymphoma cells was 71% kappa-restricted and positive for CD19, CD20, CD5, CD22, CD10, CD79a, and CD38. By immunohistochemistry, the lymphoma cells were positive for CD20, PAX-5, CD5, CD10, MUM-1, BCL-2, and negative for EBV, CD30, BCL-6, cyclin D1, SOX-11, TdT, and MYC. A high Ki-67 proliferative index of 80-90% was observed.
Cytogenetics: 47,XY,+7,del(13)(q12q22),add(14)(q32.3)(8)/46,XY(12)
Molecular studies: Negative for BCR-ABL, t(14;18), IGH, BCL-6, and MYC rearrangements
Proposed diagnosis: CD5-positive diffuse large B-cell lymphoma (DLBCL), NOS; double and triple hit rearrangements were excluded. The differential diagnosis included blastoid variant of mantle cell lymphoma and B-cell prolymphocytic leukemia.
Interesting feature(s) of submitted case: One study concludes that primary bone marrow lymphoma accounts for only 1.16% of all lymphomas and are most frequently DLBCL, as was diagnosed in our patient. He presented with characteristic features, including hepatosplenomegaly and elevated LDH. Moreover, his lymphoma cells were CD5-positive, which is often considered an important finding when diagnosing this entity.
The published literature has yet to discuss a possible correlation between primary bone marrow lymphoma and previous malignancies and their treatment. Our patient is unique, in that he was previously diagnosed with thyroid cancer and received axitinib. Moreover, EPOCH-R was administered to our patient. While no recommended therapy exists for primary bone marrow lymphoma, most studies document the use of R-CHOP, with a median survival ranging from 3.5 to 7 months. We are happy to report that our patient has currently exceeded this survival time by two months in spite of relapse.

EAHP18-BMWS-135

IgD+ classical Hodgkin lymphoma, compatible with transformation of a previously diagnosed splenic marginal zone lymphoma

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Case description: 71 year old male Caucasian patient with a history of splenic marginal zone lymphoma, diagnosed in 2015. The patient had been treated with rituximab, bendamustin and radiotherapy of the spleen. A random follow-up bone marrow trephine biopsy in July 2017 (not submitted) showed persistent lymphomatous involvement of the bone marrow (infiltration volume of 15%). A few weeks later, a guided biopsy of an intensively PET+ osteolytic focus of the Os ilium (submitted specimen) was performed and the spleen was removed.
Biopsy fixation details: 4% Formailn fixation
Frozen tissue available: no
Details of microscopic findings: Spleen (not submitted, but depicted in the accompanying PPT): The spleen weighed 1516 grams and showed infiltrates of the known splenic marginal zone lymphoma positive for CD19, CD79a, PAX5 and IgD with kappa light chain restriction, while being negative for CD20 (most probably due to the previous rituximab-therapy) and negative for cyclin D1, SOX11, CD5, CD10, BCL6, annexin A1, DBA44 and EBER. There were neither infiltrates of large cells nor of CD30 positive cells. Besides the lymphomatous infiltrate, there were also foci of extramedullary haematopoiesis.
Bone marrow biopsy of the Os ilium (submitted specimen): Diffuse infiltration of the bone marrow by a mixed infiltrate of lymphocytes, macrophages and large atypical cells with features of Hodgkin and Reed-Sternberg (HRS) cells. There is only very focal residual haematopoiesis.
Immunophenotype: HRS cells are positive for CD15, CD30, MUM1, PAX5 as well as IgD and negative for EBER, BOB1 and OCT2.
Cytogenetics: none
Molecular studies: none
Proposed diagnosis: IgD positive classical Hodgkin lymphoma, compatible with transformation of the previously diagnosed splenic marginal zone lymphoma.
Interesting feature(s) of submitted case: This case shows a focal transformation of a splenic marginal zone lymphoma into a classical Hodgkin lymphoma. The patient still has residual marginal zone lymphoma in the spleen and in the bone marrow in other locations.
Transformation of low grade lymphoma into classical Hodgkin lymphoma is known in entities such as chronic lymphocytic leukaemia or follicular lymphoma, yet in marginal zone lymphomas it is very rare. In most cases of transformed splenic marginal zone lymphoma, DLBCL or occasionally Burkitt lymphoma are observable. Outcome of transformed splenic marginal zone lymphoma tends to be poorer than that of transformed follicular lymphoma.
Hodgkin lymphoma has been reported to occur simultaneously with marginal zone lymphomas and isolated HRS-like cells can be observed in such instances, yet transformation of splenic marginal zone lymphoma into classical Hodgkin lymphoma has not been reported so far. However, the positivity for IgD in the HRS cells of our case (along with the IgD positivity of the splenic marginal zone lymphoma B-cells) strongly supports our hypothesis of transformation as conventional classical Hodgkin lymphoma lacks generally immunoglobulin- and particularly IgD expression. Due to scarcely available material of the bone marrow trephine biopsy, no further confirmatory clonality analysis was possible.
This case also illustrates the value of guided biopsies of (e.g. PET+) bone lesions as the random “blind” bone marrow trephine biopsy taken at the same time only showed involvement of the splenic marginal zone lymphoma.

EAHP18-BMWS-265

Primary bone marrow Hodgkin lymphoma masked by fulminant histiocytic infiltration and associated with massive hemophagocytic activity and hemophagocytic Lymphohistiocytosis (HLH)

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Case description: 46 years' male gentleman presented with 10 days' abdominal pain, fever and underwent ERCP and diagnosed as chronic liver disease with primary sclerosing cholangitis. Upon presentation, he was febrile, emaciated; jaundiced; looks sick; hypotensive and abdominal examination revealed hepatomegaly and ascites.

Investigations on admission: CBC revealed severe pancytopenia a total white blood cells count (WBC) 1.1 ×103/µL, neutrophil count 0.6 ×103/µL, platelet 23 ×103/µL, red blood cells (RBCs) 4.2 X 106 /µL , bilirubin 219 mg/dL, direct bilirubin 132 mg/dL, Aspartate aminotransferase (AST)152 U/L, Alanine transaminase (ALT) 42 U/L, Alkaline phosphatase(ALP) 442 U/L , Lactate dehydrogenase (LDH) 410 U/L ,urea 5.6 mmol/L ,Creatinine 52 µmol/L with high serum ferrittin more than 15000 ng/ml.

He was admitted to intensive care unit as, started on empiric broad-spectrum antimicrobial and fluid resuscitation. Virology screen result revealed EBV PCR positive (146698 IU/ml). Based on clinical and laboratory data Hemophagocytic Lymphohistiocytosis (HLH) was suspected. Methylprednisolone was started and bone marrow (BM) aspiration and biopsy requested to confirm HLH diagnosis. The patient's condition deteriorated and he developed acute kidney injury and disseminated intravascular coagulation (DIC). On day nine of admission, he went into cardiac arrest and declared death.

Meanwhile, the bone marrow biopsy result came back to confirm extensive involvement by Hodgkin Lymphoma (HL) associated with massive hemophagocytic activity.

Biopsy fixation details: BM biopsy: AZF-fixed

Frozen tissue available: Not available

Details of microscopic findings: Peripheral smear shows severe pancytopenia.

Aspirate smear is markedly hypocellular with decreased trilineage hematopoiesis. Rare histiocytes with active erythrophagocytosis were spotted.

Bone marrow biopsy architecture is distorted and shows multiple large areas of abnormal infiltrate composed almost entirely of histiocytes mixed with some T- lymphocytes within a fibrotic tissue. Residing within the histiocytic infiltrate are many large atypical cells including Reed-Sternberg cells, multinucleated giant RS cells, mononuclear Hodgkin cells, popcorn cells and lacunar cells, solitary and in sheests/clusters.

There are few residual hypocellular bone marrow spaces showing suppressed trilineage hematopoiesis and extensive infiltration with histiocytes exhibiting massive erythrophagocytic activity.

There is significant diffuse increase in reticulin fibrosis (grade 2-3 out of 3).

Immunophenotype: Immunohistochemistry:

CD30 and CD15 immunostains highlighted large sheets and clusters of Hodgkin's cells; some of which show the characteristic membrane & paranuclear dot-like positivity. These large cells show partial positivity for CD20 and PAX-5 (weak) while negative for CD79 and CD45.

The neoplastic cells resides within large sheets of histiocytes showing strong positivity for CD68, CD163 and S100.

Cytogenetics: Not done

Molecular studies: Not done

Proposed diagnosis: Classic Hodgkin lymphoma associated with massive hemophagocytosis

Interesting feature(s) of submitted case: The diagnostic challenge in this case was mainly due to clinically unsuspected lymphoma diagnosis masked by features of infection, poor general condition and lack of lymphadenopathy. In the bone marrow biopsy, HL was unexpected and rather challenging, masked by the fulminant infiltration by histiocytic cells and remarkable hemophagocytosis along with the lack of typical back ground of mixed infiltrate which is usually seen in cases of classic HL.

EAHP18-BMWS-564

Atypical presentation of B-cell lymphoma in the marrow in a patient with autoimmune background

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Case description: He had Pancytopenia and presented with a perianal abscess which became septic. Flow showed a T-cell CD4+ clone. PCR clonal expansion of T and B cells. The LDH is not raised, he has mild splenomegaly on CT (14cm), no other Lymphadenopathy
He has pan reactive RBC antibodies. He was admitted 19th/20th Jan as reacted during a red cell transfusion and dropped his Hb quickly afterwards so it was presumed he had suffered a transfusion reaction. He was started on high dose methyl pred and IVIG on 20th to manage this and had an excellent increment in platelet count and Hb increased too.
So it looks like there is some element of auto immune background. He then started R-Benda
Biopsy fixation details: 10% buffered formalin.
Frozen tissue available: No
Details of microscopic findings: Hypercellular adequate marrow with diffuse lymphoid infiltrate (CD20+) with dense admixed T-cell infiltrate and largely trilinear background haematopoiesis marked reduction in mature granulocytes. The erythroid cells show left shifted maturation with mild dyserythropoiesis. Megakaryocytes show reduced numbers but no abnormal morphological/architectural features.. Areas of streaming, suggestive of background fibrosis are noted. REticulin grade 2-3 (WHO).
Immunophenotype: FLOW CYTOMETRY BMT: 33% of WBCs are CD3+ CD4+ CD8- CD7+ CD25- CD5+ CD2+ gdTCR- T-cells with normal expression of CD5 and CD2. Please note the high CD4/CD8 ratio The majority of CD19+ cells are CD10- CD5- CD138- with no light chain expression. No expansion of CD34+ CD117+ myeloid progenitors. 1.1% of WBCs are CD138+ CD38+ CD19+ CD56- CD117- plasma cells.
Immunohistochemistry, BMT: Diffuse CD20+ (40-50% of the nucleated marrow) infiltrate that is negative for CD5, CD10, BCL6, CD23, DBA44, CD11c, CD25, TRAP, IgD and MYC protein. proliferation fraction is under 10-15%,There is no light chain restriction. Prominent accompanying CD3+ small T-cell infiltration which is predominantly CD4+ T-lymphocytes which form small loose aggregates and uneven interstitial distribution with fewer CD8+ small T-lymphocytes that are evenly scattered in the interstitium and this T-cell infiltrate is interpreted as being reactive/secondary. There is unusual pattern of TIA1 staining in some larger cells the significance of which is uncertain.
Cytogenetics: NA
Molecular studies: IgH gene rearrangement: Positive for the detection of immunoglobulin heavy chain or kappa light chain gene rearrangement(s) consistent with the presence of a clonal cell population.
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: Diffuse (40-50%) infiltration by a histologically low grade B-cell lymphma, CD5 and CD10 negative with no expression of 'hairy cell leukemia/lymphoma' markers. There is diffuse IgM expression. The differential diagnosis includes marginal zone lymphoma, lymphoplasmacytic lymphoma and low grade B-cell lymphoma, unclassifiable. Please correlate with clinical/haematological findings.
Interesting feature(s) of submitted case: No lymphadenopathy. Clinical suspicion of transfusion reaction and ?T-cell clonal expansion. No raised LDH, B-symptomas, organomegaly. Unexpected B-cell infiltrate on BMT and subsequent excellent response to IVIG and then tolerated first dose of R-Benda.