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LYMPHOMA WORKSHOP BOOK

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CONTENTS

LYMPHOMA SESSION I:
The morphological spectrum of Castleman disease and related disorders

Oral Presentations

EA4HP24-LYWS-101	Hyaline vascular Castleman disease, stroma-rich variant
EA4HP24-LYWS-273	Idiopathic Castleman disease, plasma cell variant with concurrent AA-type amyloidosis and noncaseating granulomas
EA4HP24-LYWS-153	A case of idiopathic multicentric Castleman disease-TAFRO
EA4HP24-LYWS-326	POEMS syndrome presenting with Castleman disease
EA4HP24-LYWS-301	KSHV/HHV8-associated multicentric Castleman disease with two unusual features
EA4HP24-LYWS-103	Multicentric Castleman disease with features suggestive of HHV8-positive large B-cell lymphoma vs extracavitary primary effusion lymphoma
EA4HP24-LYWS-179	KSHV/HHV8 and EBV-positive germinotropic lymphoproliferative disorder associated with Castleman disease features.
EA4HP24-LYWS-73	Follicular dendritic cell sarcoma associated with Castleman disease
EA4HP24-LYWS-20	Idiopathic multicentric Castleman disease with massive infiltration of IgG4-positive plasma cells
EA4HP24-LYWS-325	Thymic CHL masked by Castleman disease features such as extensive plasmacytosis

EA4HP24-LYWS-101

Hyaline vascular Castleman disease, stroma-rich variant

Dr. Chuan Chen, Dr. Pedro Horna, **Dr. Rebecca L. King**

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Case Description

A 35-year-old female presented with intermittent, severe left-sided abdominal pain and a 25-pound weight loss in the past three months. CT scan identified a large (7 x 11 cm) hypervascular "adrenal tumor" on the left side. While clinically suspicious for adrenocortical carcinoma, two adequate core biopsies consistently showed a bland spindle cell proliferation without evidence for malignancy. She underwent a left adrenalectomy and mass resection. A normal adrenal gland was identified, next to which was a 11 x 10 x 8 cm focally hemorrhagic, encapsulated, and partially calcified mass within the peri-adrenal fat. Lab studies showed she was HIV negative, and had normal ESR, CRP, CBC, and normal sIL6 levels.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections of the mass show multiple small follicles with regressively transformed germinal centers and concentric layering of mantle zone lymphocytes. The interfollicular areas are largely replaced by a dense spindled stromal proliferation which includes numerous hyalinizing small vessels that occasionally penetrate germinal centers. Focal cells consistent with lymphoblasts are identified within the stroma after comparing with IHC.

Immunophenotype

Follicles show prominence of follicular dendritic cells positive for CD21, CD23, CD35, and clusterin without proliferation of these markers outside of the small follicles. The stromal spindle cells are negative for CD21, CD23, CD35, clusterin, and desmin. CD31 and CD34, as well as smooth muscle actin highlight the density of small vessels but do not reveal neoplastic vascular proliferations. The stroma also shows scattered TdT positive cells consistent with T lymphoblasts. HHV8 is negative.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

1. Hyaline vascular Castleman disease, stroma-rich variant
2. Indolent T lymphoblastic proliferation

Interesting Feature(s)

Hyaline vascular Castleman disease (HVCD) exhibits a wide spectrum of morphologic findings, ranging from predominantly follicular to stromal-rich lesions. The stromal-rich variant of HVCD represents a diagnostic challenge due to its rarity and its varied cell composition in the stroma, rendering a broad differential diagnosis such as follicular dendritic cell (FDC) sarcoma and vascular neoplasms. This patient underwent two core biopsies before resection, which could have led to misdiagnosis as a vascular or other spindle cell neoplasm and represents a potential pitfall.

Of note, FDC sarcoma can arise in HVCD, presumably through a hyperplasia–dysplasia–neoplasia sequence, although in some cases it has been argued that the CD lesion is only a reaction to the FDC sarcoma rather than a precursor lesion. In our case, the morphologic (lack of cytological atypia and mitotic activity), phenotypic (negative FDC markers in the stroma), and clinical (good response to resection without recurrence or systemic therapy) features do not support FDC sarcoma or other neoplastic process.

Lastly, indolent T-lymphoblastic proliferation, marked by the scattered terminal deoxynucleotidyl transferase (TdT)+ T cells in the stroma, is not uncommon in CD. It is a benign process and should be differentiated from T-lymphoblastic lymphoma. In this case the TdT positive cells were identified only retrospectively, 10 years after initial diagnosis.In conclusion, CD has a broad spectrum of morphology and can mimic both benign and malignant proliferations. Awareness of the morphologic variations and the limitation in core-needle biopsy is crucial to avoid diagnostic pitfalls.

EA4HP24-LYWS-273

Idiopathic Castleman Disease,Plasma Cell Variant with Concurrent AA-type Amyloidosis and Sarcoidosis

Dr. Daniel Rivera[2], Dr. Hanadi El Achi[2], Dr. Amer Wahed[2], Dr. Wei Wang[3], Dr. Leonardo J. Medeiros[3], **Dr. Zhihong Hu**[1]

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Case Description

A 62-year-old woman, with history of type 2 diabetes, hypothyroidism, Plummer-Vinson syndrome, and previously known lymphadenopathy in the porta cava region, presented with symptoms of fatigue and dysphagia. A CT scan of the abdomen revealed stable lymphadenopathy, with a 2.0 cm supra-pancreatic, 2.0 cm hepatic artery, and 5.0 cm porta hepatis lymph node, consistent with findings from imaging five years ago. Additionally, new areas of calcified granulomas were identified in the liver, spleen, and the base of the right lung.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

Not performed

Details of Microscopic Findings

Histopathological examination of the excised portal and supra-pancreatic lymph nodes revealed variably sized follicles distributed in the cortex and medulla. Many exhibited deposits of amorphous eosinophilic material at the center of the follicles, accompanied by mantle zone hyperplasia and an 'onion-skin' appearance. Sheets of mature plasma cells infiltrated the interfollicular regions and medulla, along with interfollicular vascular hyperplasia featuring occasional hyalinized blood vessels penetrating the follicles. Additionally, focal distinct non-caseating granulomas were present, containing rare giant cells and asteroid bodies. Immunohistochemistry (IHC) for IgG4 highlighted fewer than 10% of IgG+ plasma cells, and the HHV8 stain was negative. Flow cytometry analysis revealed a polytypic plasma cell population, with no aberrant B or T cells identified. Furthermore, Congo-red stain demonstrated apple-green birefringence in areas with eosinophilic deposits. Consequently, IHC for serum amyloid A (SAA) protein and liquid chromatography-tandem mass spectrometry (LC-MS/MS) confirmed AA-type amyloid. Tests for acid-fast bacilli (AFB) and fungal organisms, using AFB and GMS staining, respectively, yielded negative results. In situ hybridization confirmed the presence of polytypic plasma cells, and rare small cells were positive for Epstein-Barr virus-encoded small RNA (EBER).

Immunophenotype

Flow cytometry analysis revealed a polytypic plasma cell population, with no aberrant B or T cells identified.

Cytogenetics

Not performed

Molecular Studies

PCR analysis was negative for monoclonal IGH and TRB/TRG rearrangements.

Proposed Diagnosis

Idiopathic Castleman disease, plasma cell variant with concurrent AA type amyloidosis and sarcoidosis.

Interesting Feature(s)

To our knowledge, this case represents the first documented occurrence of concurrent idiopathic Castleman disease, amyloidosis, and sarcoidosis. Interleukin-6 (IL-6) is critical in Castleman disease with multisystemic impact and B and T-cell activation. High IL-6 levels have been detected in sarcoidosis, playing a role in inflammation, and leading to non-caseating granulomas. It may suggest that IL-6 could be the pathophysiologic link between these two disorders. In this case, we depict a chronic inflammatory state resulting from Castleman disease and sarcoidosis, driven by persistently elevated IL-6 levels. This supports the overproduction of SAA protein, contributing to disease progression and the manifestation of secondary reactive amyloidosis. Given that SAA protein may play a pathogenic role in the granulomatous inflammation of sarcoidosis through a sustained inflammatory reaction, the increased SAA, coupled with Castleman disease, likely exacerbated sarcoidosis in this patient.

EA4HP24-LYWS-153

A Case of Idiopathic Multicentric Castleman Disease-TAFRO

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Case Description

A 58-year-old female presented for follow-up of chronic inflammatory demyelinating polyneuropathy, hemophagocytic lymphohistiocytosis (HLH), hypothyroidism, and pancytopenia. A bone marrow (BM) biopsy at the time of HLH diagnosis had showed mildly increased megakaryocytes and reticulin fibrosis without cytogenetic or molecular genetic abnormalities. After 13 months of treatment with intravenous immunoglobulin (IVIG), she presented with fatigue, lightheadedness, anasarca, acute kidney injury, pancytopenia, and fever. PET showed widespread FDG-avid lymphadenopathy and splenomegaly. Core needle biopsy of a left external iliac lymph node showed reactive changes and polytypic plasmacytosis HIV and HHV-8 serologic testing were negative. An excisional biopsy of the right axillary lymph node was performed.

Biopsy Fixation Details

A portion was submitted in formalin; the remaining tissue was submitted in B+ fixative.

Frozen Tissue Available

-

Details of Microscopic Findings

The specimen was a slightly enlarged lymph node with preserved architecture. There were scattered lymphoid follicles, most with small involuted germinal centers and well-defined mantle zones. The interfollicular area was occupied by small lymphocytes, occasional immunoblasts, and many plasma cells. The plasma cells were mostly small and mature but there were occasional enlarged multinucleated forms. The interfollicular compartment showed increased vascularity. Sinuses were patent and showed sinus histiocytosis with some histiocytes showing erythrophagocytosis.

Immunophenotype

Flow cytometry did not show an abnormal B- or T-cell population. Immunostains showed many PAX5+ B cells, mainly in follicles. Many germinal centers had decreased numbers of B cells. CD21 showed dense follicular dendritic cell meshworks associated with follicles with a suggestion that there were increased follicular dendritic cells in those germinal centers with decreased B cells. Germinal centers were negative for BCL2. Kappa and lambda immunoglobulin light chains showed many polytypic plasma cells. IgM, IgA, and IgG4 each stained scattered plasma cells. Most plasma cells were IgG+. There was no staining for HHV8. CD123 mainly delineated vascular spaces, including sinuses; plasmacytoid dendritic cells were not conspicuous.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

Reactive lymphoid hyperplasia with small, involuted germinal centers and prominent plasmacytosis, suggestive of idiopathic multicentric Castleman disease (iMCD).

Interesting Feature(s)

The patient had a long history of inflammatory symptoms without a known etiology (but did meet diagnostic criteria for HLH), and the symptoms only partially resolved after treatment with corticosteroids and IVIG. After a diagnostic excisional lymph node biopsy and continued evolution of symptoms, it became clear that the patient's presentation was most consistent with iMCD-TAFRO (thrombocytopenia, anasarca, fever/inflammatory symptoms, renal dysfunction, BM reticulin fibrosis, organomegaly). However, given the presence of demyelinating polyneuropathy, splenomegaly, and hypothyroidism, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin findings) syndrome was also considered; however, there was no evidence of a plasma cell neoplasm. The overlap in symptomatology points to the need for a robust diagnostic workup; it may take multiple bone marrow or lymph node biopsies to render a definitive diagnosis. The patient was treated with siltuximab and prednisone with excellent response and resolution of lymphadenopathy and splenomegaly.

EA4HP24-LYWS-326

POEMS syndrome presenting with Castleman disease

Dr. Ion Prisneac[1], Dr. Stephanie Wright[2], Dr. Gustavo Torres[1]

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Case Description

A 44-year-old female was found to have bilateral inguinal, iliac, and retroperitoneal lymphadenopathy following a GYN visit for menorrhagia. An excisional biopsy of the left inguinal lymph node (LN) was performed to rule out metastatic carcinoma, followed by a bone marrow biopsy for staging/diagnosis.

Biopsy Fixation Details

LN tissue was submitted in 10% buffered formalin. The bone marrow core biopsy was submitted in 10% buffered formalin and decalcified in hydrochloric acid. Additional LN and bone marrow tissues were submitted in RPMI for flow cytometry.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The LN is enlarged and shows angiofollicular lymphoid hyperplasia. The lymphoid follicles demonstrate atretic germinal centers comprised predominantly of follicular dendritic cells, surrounded by layers of mantle-type cells (onion-skinning). Several follicles show penetrating, hyalinized blood vessels, and "twinning". The interfollicular areas are expanded by sheets of plasma cells. These findings are compatible with Castleman disease with mixed features of hyaline vascular and plasma cell variants. The bone marrow biopsy showed a cellular marrow with a small lymphoid aggregate surrounded by plasma cells and a mild megakaryocyte hyperplasia.

Immunophenotype

LN flow cytometry was unremarkable. Immunohistochemical (IHC) stains performed on the lymph node showed an essentially normal staining pattern of the follicles. The interfollicular plasma cells are positive for CD138, MUM1, and IgA, are lambda light-chain restricted and show weak/focal coexpression with CD19 and CD45. A subset of plasma cells express IgG with no increase in IgG4-positive plasma cells. The plasma cells are negative for cyclin D1, IgM, and IgD. HHV8 and EBV-ISH are negative. Bone marrow identified CD19-negative, lambda light chain-restricted monotypic plasma cells.

Cytogenetics

Chromosome analysis revealed a normal female karyotype (46, XX [20]). Bone marrow plasma cell FISH showed chromosomes 13 and 14 monosomies.

Molecular Studies

A clonal immunoglobulin gene rearrangement was detected by PCR on the LN tissue. A hematological panel (DNA sequencing of 406 genes and RNA sequencing of 265 genes) detected no reportable genomic alterations, however, twelve variants of unknown clinical significance were found.

Mass spectrometry performed on the bone marrow aspirate found a small monoclonal IgA lambda M-protein. Vascular endothelial growth factor (VEGF) > 700 pg/mL (reference ≤ 96.2), Interleukin-6 = 2.6 pg/mL (reference <6.4).

Proposed Diagnosis

Lymph Node, Left Inguinal, Excisional Biopsy: IgA-lambda light chain restricted monotypic plasma cells in a background of Castleman disease with mixed hyaline vascular and plasma cell features, with a comment to that these features are most often seen in POEMS syndrome.

A subsequent bone marrow biopsy showed a low-level involvement by CD19-negative lambda light chain restricted monotypic plasma cells (5-10% by CD138 IHC).

Interesting Feature(s)

Following the LN biopsy, the patient was further evaluated and diagnosed with polyneuropathy and skin changes, markedly elevated VEGF, and low-level marrow involvement by CD19-negative, lambda light chain restricted monotypic plasma cells. POEMS syndrome is usually diagnosed starting from a clinical suspicion, however, in this case, the LN histopathologic findings prompted additional workup that facilitated the clinical diagnosis. Multicentric Castleman disease usually presents with plasma cell variant or mixed features and, when KSHV/HHV8-negative, raises the possibility of a plasma cell dyscrasia leading to clonality testing.

EA4HP24-LYWS-301

KSHV/HHV8-associated multicentric Castleman disease with two unusual features

Dr. Juliette Fontaine, Dr. Marie Donzel, Prof. Alexandra Traverse-Glehen

Hospices Civils de Lyon, Pathology, Pierre Bénite, France

Case Description

A 75-year-old man without any relevant medical history presented with altered general condition and night sweats. CT scan showed a polyadenopathy. Broad infectious workup was negative, including HIV serology. A surgical lymph node biopsy was performed.

Biopsy Fixation Details

Neutral buffered formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

Two lymph nodes measuring 2 x 2.5 cm and 2.5 x 3.5 cm were analyzed. The architecture was preserved. The germinal centers varied in size ; some had a slightly "regressive" appearance. The mantle zone was more or less thickened, sometimes with a "single file" arrangement of cells. They were made up of small lymphocytes with dense chromatin. In some follicles, a vessel was seen penetrating the germinal centre through the mantle zone. The interfollicular area were made up of a polymorphous cell population with a majority of small lymphocytes, mixed with plasma cells and rare large scattered cells. Numerous vessels were seen. Focally, on slide 2A, numerous large cells with a plasmablastic appearance were seen on a few mantle zones, sometimes occupying the entire area of the mantle zone, but with a preserved architecture.

Immunophenotype

There was a preserved distribution of B and T cells zones. The immunohistochemical study confirmed the normal phenotype of the germinal centers. It also highlighted the regressive appareance of some germinal centers, whith follicular dendritic cell prominence. The anti-CD38 antibody confirmed the presence of numerous polytypic plasma cells. The anti-HHV8 antibody highlighted a few cells in the mantle zones. Eber RNA *in situ* hybridization revealed a large number of cells in rare germinal centers and a few cells scattered in the interfollicular region distinct from HHV8+ cells.

The plasmablastic cells observed in a few mantle zones (slide 2A), expressed CD38 and HHV8 and displayed lambda monotypia. They did not express CD20, weakly and partially expressed CD79a, and did not express Eber RNA by *in situ* hybridization. The Ki-67 proliferation index was high in these areas, around 70%.

Cytogenetics

No

Molecular Studies

The lymphocyte clonality was carried out (1) on a whole section (block 01A), (2) after macrodissection of the plasmablast-rich area (block 02B). On the whole section, there was no immunoglobulin receptor gene rearrangement. On the macrodissected area, there was an immunoglobulin receptor gene rearrangement with a moderate intensity.

Proposed Diagnosis

KSHV/HHV8-associated multicentric Castleman disease with two unusual features, difficult to interpret : (1) an area with numerous HHV8+/EBER- monotypic lambda plasmablasts, but which remain limited to the mantle zones, with a preserved architecture. Despite the presence of an immunoglobulin receptor gene rearrangement, these aspects do not seem sufficient to retain the diagnosis of focal KHSV/HHV8 positive diffuse large B-cell lymphoma, (2) some germinal centres contain numerous EBV+ cells but do not correspond to HHV8+ germinotropic lymphoproliferation (cf EBV+/HHV8- cells, no obvious atypia) and are probably related to the EBV cycle (EBV reactivation ?).

Interesting Feature(s)

(1) The difficulty to interpret the area with numerous HHV8+ plasmablasts: diagnostic and prognostic value? Should the term microlymphoma be used? (2) How to interpret EBV+/HHV8- cells in germinal centers ? Do they indicate associated-EBV reactivation? For this patient we did not know the value of the EBV viral load in blood.

Patient was treated with Rituximab and Valacylovir, with a good evolution. Eighteen months later, he died following coronary bypass surgery.

EA4HP24-LYWS-103

Multicentric Castlemen disease with features suggestive of HHV8-positive large B-cell lymphoma vs extracavitary primary effusion lymphoma

Qing Chen, Hamza Tariq, Lucy Fu, Kristy Wolniak, Barina Aqil, Juehua Gao, Yi-Hua Chen

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Case Description

69-year-old man with well-controlled HIV, presenting with shortness of breath (SOB), small loculated pleural effusion and diffuse lymphadenopathy (neck, mediastinum and abdomen/pelvis); no significant B symptoms. Neck lymph node (LN) biopsy showed features of multicentric Castleman disease (MCD) and clusters of HHV8+/EBV-/lambda-large pleomorphic cells, concerning for HHV8+ diffuse large B-cell lymphoma (DLBCL) vs primary effusion lymphoma (PEL). Thoracentesis removed minimal fluid; cytology showed few HHV8+ large atypical cells. He received rituximab x 8 weekly and achieved good partial response. One year later, he noted SOB, low energy, progressive lymphadenopathy.

Another LN biopsy showed MCD and more abundant HHV8+ pleomorphic cells, favor DLBCL. He received CHOP x 6 cycles and achieved near complete response by PET. He has had no evidence of recurrence to date (18 months after CHOP).

Biopsy Fixation Details

10% neutral-buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Neck lymph node biopsy showed partially preserved architecture with scattered follicles, some with reactive germinal centers and others with atrophic hyalinized germinal centers. The interfollicular area was expanded with increased plasma cells. Notably, there were multiple clusters of pleomorphic, anaplastic-appearing large cells with irregular/multilobated nuclei, vesicular chromatin, prominent nucleoli, and abundant basophilic cytoplasm (see submitted photos). The large cells were often seen around follicles and focally in subcapsular sinusoids. Confluent sheets of large cells were not present. The second LN biopsy one year later showed similar findings but more abundant large atypical cells. The pleural fluid showed few HHV8+/EBER- atypical cells.

Immunophenotype

By immunohistochemistry, the atypical cells were positive for HHV8, CD138 and MUM1, but negative for CD20, CD79a, EBER-ish, kappa/lambda, IgM/IgG, BCL6, CD3, CD30 and all other B and T cell markers. The background plasma cells were polytypic; no apparent lambda+ plasmablasts were noted. Flow cytometry revealed polytypic B cells and unremarkable T cells.

Cytogenetics

FISH negative for rearrangements of *BCL6* and *BCL2*, and *IGH::MYC* fusion; positive for *MYC* rearrangement

Molecular Studies

Negative for clonal *IGH* rearrangement

Proposed Diagnosis

HHV8-associated lymphoproliferative disorder, multicentric Castleman disease and clusters of highly atypical cells, concerning for HHV8+ large B-cell lymphoma vs primary effusion lymphoma

Interesting Feature(s)

This case has several interesting features.

1. While the overall morphologic and clinical findings are consistent with MCD, the HHV8+ cells are highly atypical with an anaplastic rather than plasmablastic morphology, and an unusual phenotype (CD138+, kappa/lambda-, IgM/IgG-, lack all B-cell markers), which is not typical of HHV8+ MCD/DLBCL but suggestive of PEL/extracavitary PEL. But the extensive lymphadenopathy with MCD features, lack of EBER and minimal effusion are not characteristic of PEL. A distinction is challenging.
2. The marked morphologic atypia and sinusoidal infiltrate of HHV8+ large cells are concerning for DLBCL, but the lack of confluent sheets of large cells and effacement of nodal architecture make a definitive diagnosis of DLBCL difficult.

3. Another interesting aspect of this case is that the patient has a relatively indolent clinical course and no overt B symptoms. This case may represent a distinct HHV8-associated lymphoproliferative disorder with features of MCD and focal involvement by EBV-negative PEL, and is associated with relatively good prognosis in well-controlled HIV patient.

EA4HP24-LYWS-179

KSHC/HHV8 and EBV-positive germinotropic lymphoproliferative disorder associated with Castleman Disease features.

Dr. Luisa Lorenzi[1], Dr. Giulio E. Mandelli[1], Dr. Matteo Simbeni[1], Dr. Silvia Lonardi[1], Dr. Mattia Bugatti[2], Dr. Marco Chiarini[2], Dr. Mattia Facchetti[2], Dr. Iacopo Ghini[2], Dr. Flavia Melotti[2], Dr. Alessandro Re[2], Prof. Fabio Facchetti[1], Prof. William Vermi[1]

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Case Description

An otherwise healthy, immunocompetent, Italian, 67-year-old man presented with isolated lymphadenopathy at the right axilla. No pleural effusion or evidence of other adenopathies were identified at imaging. A fine needle biopsy was performed in the clinical suspicion of lymphoma. At histology, the biopsy revealed isolated aggregates of CD3+ atypical cells, with plasmacytoid appearance, in an otherwise normal lymphoid parenchyma. Excision of the whole lymph node was indicated.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

Yes (snap frozen and cell suspensions)

Details of Microscopic Findings

The lymph node, with a maximum diameter of 5 cm, shows thin capsule, obliterated marginal sinus, and parenchyma characterized by prominent vascularity, occasional thin sclerotic bands, mature plasmacytosis and follicles with heterogenous morphology. The latter often display regressive features with onion-skin-like mantles, lympho-depleted germinal centers (GC), penetrated by radially oriented hyalinized blood vessels; multiple GC surrounded by a single mantle are also evident. In the context of the follicles, either in the mantle or in the center, aggregates of atypical large cells are present. They show round to oval nuclei, prominent nucleoli and large amphophilic, occasionally eccentric, cytoplasm. Cells with the same morphology are evident in the lumen of some sinuses.

Immunophenotype

Atypical cells are characterized by co-infection by EBV (EBER) and HHV8 (ORF73); they are positive for CD38 and MUM1, negative for CD138; B-cell markers CD20 and CD79a are

heterogeneously expressed, PAX5 and CD19 are completely negative. Aberrant expression of T cell markers CD3 and ZAP70 is evident (negative CD2, CD5, CD4 and CD8). Follicular dendritic cells (FDC) markers (CD21, CD23) highlight the intermingling of atypical cells in FDC networks and an onion-skin like pattern of follicle mantles. Internodular mature plasma cells show polytypic expression of Ig light chains, with no increase in the IgG4 fraction. Plasmacytoid dendritic cells (CD123+ BDCA2/CD303+) are evident in the internodular areas, sparce or in small clusters.

Cytogenetics

Not performed.

Molecular Studies

IGH gene rearrangement analysis by PCR showed a polyclonal profile. RNAscope for immunoglobulin light chains transcript highlights monotypic lambda gene expression on a fraction of atypical cells, kappa being negative in all.

Targeted NGS analysis is on going.

Proposed Diagnosis

KSHC/HHV8 germinotropic lymphoproliferative disorder

Interesting Feature(s)

In our opinion this is a rare case of KSHC/HHV8 germinotropic lymphoproliferative disorder (GLPD), characterized by association with Castleman disease (CD) features. This association was previously reported and supports the hypothesis of a morphological continuum in the group of diseases associated with HHV8 infection. Indeed, in this case, atypical plasmablasts were found in the germinal center as well as in mantles, recalling HHV8+ Multicentric CD, and in sinusoids, questioning the differential diagnosis with an extracavitary PEL. However, interfollicular polytypic plasmacytosis, CD3 aberrant expression, CD138 negativity and polytypic IGH rearrangement are in favor of GLPD. This patient is alive with no evidence of disease three months after diagnosis without therapeutical intervention.

EA4HP24-LYWS-73

Follicular dendritic cell sarcoma associated with Castleman Disease

Dr. Siok-Bian Ng[1,2], Dr. Char-Loo Tan[2], Dr. Kong-Bing Tan[1,2]

[1] National University of Singapore, Yong Loo Lin School of Medicine, Department of Pathology, Singapore, Singapore; [2] National University Health System, Department of Pathology, Singapore, Singapore

Case Description

- A 57-year-old Chinese female presented with stridor and respiratory obstruction. She had previous history of goiter diagnosed on ultrasound.

- An emergency total thyroidectomy was performed to relieve airway obstruction. Intra-operatively, there was a large tumour displacing the thyroid gland. Total thyroidectomy performed.
- Post-operative PET-CT scan revealed enlarged mediastinal lymph nodes and bronchoscopy identified a polypoidal tracheal tumour which was resected.
- The patient was negative for HIV and HHV8-PCR.
- BM biopsy was negative for tumour.

Biopsy Fixation Details

Specimen fixed in 10% buffered formalin

Frozen Tissue Available

Nil

Details of Microscopic Findings

- Tumour composed of spindle to ovoid cells in sheets, fascicles and storiform whorls. Neoplastic cells revealed dispersed chromatin and small nucleoli.
- Dense lymphoplasmacytic infiltrate, imparting an inflammatory pseudotumour-like appearance
- Myxoid areas with dyscohesive tumour cells
- Brisk mitotic activity.
- Residual lymph node tissue at periphery showed:
    - Scattered atretic follicles, penetration by prominent central vessels with hyalinized walls and plump endothelial cells
    - Some follicles surrounded by concentric layers of small lymphocytes
    - Proliferation of FDCs outside residual follicles with hyperplastic / dysplastic features

Immunophenotype

• The tumour cells are positive for CD23, CD21, CD35, podoplanin, CXCL13, S100, EMA. They also show focal and patchy staining for desmin (IMT-like areas) and SMA (myxoid area).
• The tumour cells are negative for ALK1, CD34, EBER-ISH, AE1/3, CAM5.2.
• Podoplanin and CD35 also highlight the follicular dendritic proliferations in residual lymph node tissue at the periphery.
• The lymphocytes are mostly CD20+ B cells and fewer CD3+ T cells
• Scattered immature TDT+ cells present..

Cytogenetics

Nil

Molecular Studies

Nil

Proposed Diagnosis

Follicular dendritic cell sarcoma associated with Castleman disease, hyaline vascular variant.

Interesting Feature(s)

1. Follicular dendritic cell sarcoma (FDCS) is associated with hyaline-vascular Castleman disease (HV-CD) in a subset of cases (<20%). HV-CD can precede or co-occur with FDCS.
2. As illustrated in this case, possible transition with proliferation of dysplastic FDCs outside the follicles can be observed in some cases of FDCS.

3. A hyperplasia–dysplasia–neoplasia model of FDC proliferation has been proposed for the link between hyaline-vascular Castleman disease and FDCS.

References:
1. Li A, Khoo KL, Tan CL, Pang A, Lee P. Lymphadenopathy and upper airway obstruction. Am J Respir Crit Care Med. 2015 Jan 1;191(1):e1-3. PMID: 25551354.
2. Sun X, Chang KC, Abruzzo LV, Lai R, Younes A, Jones D. Epidermal growth factor receptor expression in follicular dendritic cells: a shared feature of follicular dendritic cell sarcoma and Castleman's disease. Hum Pathol. 2003 Sep;34(9):835-40.
3. Chan AC, Chan KW, Chan JK, Au WY, Ho WK, Ng WM. Development of follicular dendritic cell sarcoma in hyaline-vascular Castleman's disease of the nasopharynx: tracing its evolution by sequential biopsies. Histopathology. 2001 Jun;38(6):510-8.
4. Facchetti F, Lorenzi L. Follicular dendritic cells and related sarcoma. Semin Diagn Pathol. 2016 Sep;33(5):262-76. PMID: 27318412.5. Facchetti F, Pileri SA, Lorenzi L, Tabanelli V, Rimsza L, Pittaluga S, Dirnhofer S, Copie-Bergman C, de Leval L, Rosenwald A, Wotherspoon A, Fend F. Histiocytic and dendritic cell neoplasms: what have we learnt by studying 67 cases. Virchows Arch. 2017 Oct;471(4):467-489. PMID: 28695297

EA4HP24-LYWS-20

Idiopathic multicentric Castleman disease with massive infiltration of IgG4-positive plasma cells

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Case Description

A 69-year-old male presented with bilateral inguinal, axillary, and intrapelvic lymphadenopathy. No remarkable systemic symptoms were recognized. Clinically, no masses such as in the salivary gland or orbit - representative affected organs in IgG4-RD - were detected other than lymphadenopathy. The inguinal lymph node was excised.

Laboratory data:
WBC 5600/ml (no atypical cells, eosinophils 1.8%), Hb 12.2 g/dl, Plt 28.7x10^4/ml, LD 112 U/l, sIL2R 1000 U/ml (normal range, 121-613), TP 9.4 g/dl, Alb 3.8 g/dl, IgG 3485 mg/dl (870-1700), IgG4 802 mg/dl (11-121), IgA 347 mg/dl (110-410), IgM 88 mg/dl (31-200), IL6 8.4 pg/ml (<7), CRP 0.87 mg/dl, ESR 116 mm/h (0-15), Anti-HIV antibody (-), Anti-HTLV-1 antibody (-)
Imaging:
PET/CT: FDG accumulation was identified in the bilateral inguinal, axillary, and intrapelvic lymph nodes.

Clinical course:
As there were no severe symptoms, no treatment was given, and careful observation is now in progress.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The lymph node shows a preserved architecture. Diffuse sheet-like infiltration of mature plasma cells is evident surrounding regressed or hyperplastic follicles. Hemosiderin deposits are scattered while eosinophil infiltration is not evident. No significant proliferation of fibroblasts forming a storiform pattern – which is frequently observed in IgG4-related disease (IgG4-RD) - was identified.

Immunophenotype

In the lymph node, lymph follicles were positive for CD20, and plasma cells surrounding follicles were positive for CD138. Numerous IgG- and IgG4-positive plasma cells were recognized, and IgG4/IgG ratio was about 0.5. No light chain restriction was observed. Flowcytometric analysis did not identify any abnormal phenotypes. No cells positive for HHV-8 (LANA) or in situ hybridization for EBV-encoded small RNA (EBER) were detected.

Cytogenetics

46,XY[4]

Molecular Studies

Not done

Proposed Diagnosis

Idiopathic multicentric Castleman disease (iMCD), NOS with elevated serum IgG4 levels and abundant IgG4-positive plasma cells in the lymph node

Interesting Feature(s)

This case shows borderline clinicopathological findings between IgG4-RD and HHV8-negative idiopathic multicentric Castleman disease (iMCD). Even though the IgG4/IgG ratio was almost 0.5 in the lymph node, a diagnosis of iMCD was favored over IgG4-RD based on the histological findings, such as diffuse sheets of plasma cells, hemosiderin-laden histiocytes, and lack of eosinophil infiltration. Clinical findings of multiple lymphadenopathies, elevated ESR, and polyclonal gammopathy satisfied the diagnostic criteria of iMCD[1].

The elevation of serum IgG4 and obvious infiltration of IgG4-positive plasma cells were often observed in iMCD[2]. Fifteen of 534 (2.8%) cases of IgG4-related disease showed the characteristics of both IgG4-RD and MCD histologically, called IgG4-CD[3]. Furthermore, the present case was considered to suit the diagnosis of idiopathic plasmacytic lymphadenopathy (IPL), a clinicopathological subtype of iMCD. IPL usually corresponds to the iMCD-non TAFRO type, with better prognosis compared with the TAFRO type. This case is the first iMCD-IPL case with a high amount of IgG4 plasma cells. A comprehensive integration of clinicopathological findings is required for an accurate diagnosis.

EA4HP24-LYWS-325

Thymic CHL masked by Castleman disease features such as extensive plasmacytosis

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Case Description

69-year-old female patient presenting with a thymic mass. The lesion was found by a full body CT scan during the course of investigations for an inflammatory syndrome. The CT scan found no other lymphadenopathies or anomalies.

An excision of the thymic nodule was performed.

Macroscopy: the lesion weighted 50 gr and measured 8.5 x 5 x 3.5 cm. It had a lobulated architecture with a light brown color.

Biopsy Fixation Details

Formol

Frozen Tissue Available

no

Details of Microscopic Findings

focal follicular hyperplasia with some other follicles showing depletion of the centrofollicular area; the mantle zones had a variable thickness with no « onion skin » appearance; extensive polytypic plasmacytosis; focal rare cells that had a Reed-Sternberg, mummified or lacunar morphology

Immunophenotype

the Reed-Sternberg cells were CD20-, CD30+, CD15, PAX5+ (dim). The plasmocytes were polytypic for kappa and lambda. EBER and HHV8 were negative.

Cytogenetics

no

Molecular Studies

no

Proposed Diagnosis

thymic localization of a classical Hodgkin lymphoma with Castleman features such as extensive plasmacytosis

Interesting Feature(s)

rarity of Reed-Sternberg cells masked by an extensive plasmacytosis; the diagnosis of an unicentric Castleman disease plasma cell type should warrant the exclusion of a masked lymphoma (especially CHL)

Cases discussed by the panel

EA4HP24-LYWS-9	KSHV/HHV8-associated multicentric Castleman disease with fulminant clinical course
EA4HP24-LYWS-10	Idiopathic multicentric Castleman disease-TAFRO syndrome
EA4HP24-LYWS-28	A strange "follicular lymphoma"
EA4HP24-LYWS-48	A case of HHV-8 associated multicentric Castleman disease and multifocal Kaposi sarcoma
EA4HP24-LYWS-53	A case of Castleman disease, plasmacytic variant, with cytogenetic clonal aberration
EA4HP24-LYWS-56	23-year-old man with idiopathic multicentric Castleman disease, NOS
EA4HP24-LYWS-62	Follicular lymphoma with hyaline-vascular Castleman-like features.
EA4HP24-LYWS-68	HIV-associated HHV8-positive multicentric Castleman disease with concurrent Kaposi sarcoma
EA4HP24-LYWS-71	Idiopathic multicentric Castleman disease, HHV8-negative, with increased IgG4-positive plasma cells
EA4HP24-LYWS-78	HHV-8-associated multicentric Castleman disease and Kaposi sarcoma in a 70-year-old HIV-negative man
EA4HP24-LYWS-82	Splenic involvement in HHV8-related multicentric Castleman disease.
EA4HP24-LYWS-99	Diagnostic mimic of multicentric Castleman disease in a Lymph Node of a 76-year-old woman with Schnitzler syndrome
EA4HP24-LYWS-106	IgG4-related lymphadenopathy mimicking Casteman disease, hyaline vascular variant
EA4HP24-LYWS-111	HHV-8 positive multicentric Castleman disease presenting with hemophagocytic lymphohistiocytosis
EA4HP24-LYWS-114	Castleman disease (iMCD?) with follicular neoplasia in situ in the setting of long lasting SAPHO syndrome
EA4HP24-LYWS-118	EBER and HHV8 (+) high grade B cell lymphoma with multicentric Castleman like features arising in the setting of immunodeficiency
EA4HP24-LYWS-128	HHV8+ plasma cell variant of Castleman disease with concurrent Kaposi sarcoma
EA4HP24-LYWS-141	Paraneoplastic Castleman disease like histopathological features in plasma cell neoplasia/POEMS syndrome.
EA4HP24-LYWS-143	Multicentric Castleman's disease (MCD) with HHV8+/EBV+ plasmablastic proliferation.
EA4HP24-LYWS-146	86-year-old HIV+ man with KSHV+ multicentric Castleman disease and primary effusion lymphoma
EA4HP24-LYWS-147	Follicular dendritic cell sarcoma arising from Castleman disease, hyaline vascular variant, in a 60-year-old female
EA4HP24-LYWS-155	Follicular dendritic cell (FDC) sarcoma arising from hyaline vascular-unicentric Castleman disease (HV-UCD) with TdT+ cells present.

EA4HP24-LYWS-157	HHV-8-positive, HIV-negative, multicentric Castleman disease with simultaneous lymph node Kaposi sarcoma.
EA4HP24-LYWS-159	HHV8 negative Castleman disease, mixed hyaline vascular variant and plasma cell variant, stroma-rich, with progression to B-cell lymphoma
EA4HP24-LYWS-163	TAFRO variant of idiopathic multicentric Castleman disease
EA4HP24-LYWS-169	EBV-associated reactive hyperplasia with Castleman-like features and subsequent progression to classic Hodgkin lymphoma
EA4HP24-LYWS-171	Kaposi sarcoma and concomitant KSHV-associated multicentric Castleman disease (KSHV-MCD) in the setting of HIV infection.
EA4HP24-LYWS-181	BCL2-R-negative CD23-positive follicle center lymphoma with Hyaline-Vascular Castleman Disease-like features
EA4HP24-LYWS-185	Monoclonal plasma cell proliferation in a case of Castleman disease
EA4HP24-LYWS-197	KSHV+ large B-cell lymphoma with EBV co-infection arising from multicentric Castleman disease (MCD) with concurrent Kaposi sarcoma (KS)
EA4HP24-LYWS-199	Hyaline-vascular Castleman disease with exuberant stromal/vascular proliferation
EA4HP24-LYWS-205	Follicular dendritic cell sarcoma associated with hyaline-vascular Castleman disease – A case report
EA4HP24-LYWS-213	Lymph node with simultaneous involvement by HHV8+ multicentric Castleman disease and Kaposi sarcoma
EA4HP24-LYWS-217	Retroperitoneal unicentric Castleman disease, hyaline vascular variant associated with thymoma: are they pathologically related? The old link is revive
EA4HP24-LYWS-224	Unravelling importance: exploring a rare stroma-rich variant of hyaline-vascular Castleman disease
EA4HP24-LYWS-225	Features of KSHV/HHV8-associated multicentric Castleman disease in the setting of simultaneous widely metastatic Kaposi sarcoma
EA4HP24-LYWS-235	Hyaline vascular variant of Castleman disease presenting as a peri-pancreatic mass
EA4HP24-LYWS-245	Unicentric Castleman-disease
EA4HP24-LYWS-249	Diagnosis of an idiopathic multicentric Castleman disease – TAFRO case
EA4HP24-LYWS-251	Castleman disease in 16-years-old female patient with cervical lymphadenopathy
EA4HP24-LYWS-255	A case report: HHV8 (+) multicentric Castleman disease
EA4HP24-LYWS-257	2 Cases of POEMS-associated multicentric Castleman Disease with bone marrow involvement
EA4HP24-LYWS-258	Unusual case of Castleman disease, plasma cell variant involving nasopharynx having monotypic plasma cells with kappa light chain restriction

EA4HP24-LYWS-260	Follicular dendritic cell sarcoma arising from a background of Castleman disease, Hyaline-Vascular variant
EA4HP24-LYWS-261	Castleman disease, plasma cell variant, with IgA lambda restricted plasma cells, associated with underlying plasma cell neoplasm
EA4HP24-LYWS-271	Unicentric Castleman disease, hyaline vascular subtype, with prominent follicular dendritic cell proliferation in a peripancreatic mass
EA4HP24-LYWS-275	Idiopathic multicentric Castleman disease (iMCD)-TAFRO variant, diagnosed in the bone marrow
EA4HP24-LYWS-281	KSHV/HHV-8-associated multicentric Castleman disease in an HIV+ individual.
EA4HP24-LYWS-282	KSHV/HHV8-associated multicentric Castleman disease and nodal Kaposi sarcoma displaying a lymphangiectatic pattern in an HIV+ individual.
EA4HP24-LYWS-300	KSHV/HHV8-associated multicentric Castleman disease and Kaposi sarcoma in a same lymph node.
EA4HP24-LYWS-309	HHV8-associated multicentric Castleman disease with concomitant Kaposi sarcoma and disseminated histoplasmosis
EA4HP24-LYWS-312	IgG4-related disease overlapping with an early hyaline Castleman disease
EA4HP24-LYWS-316	Atypical IgG4+ Lymph-node plasmacytic proliferation
EA4HP24-LYWS-318	Hyaline vascular-type unicentric Castleman disease (HV-UCD) with probable *SRP72* germline mutation
EA4HP24-LYWS-332	Pediatric in situ lymphoma and Castleman disease – possibility for progression or presence of synchronous diseases
EA4HP24-LYWS-334	B-cell marker silent large B-cell lymphoma HHV-8+ arising in a patient with multicentric Castleman disease
EA4HP24-LYWS-341	Follicular dendritic cell sarcoma arising in a background of Castleman disease
EA4HP24-LYWS-342	HHV8-related multicentric Castleman's disease with EBV coinfection and reactivation
EA4HP24-LYWS-362	Unicentric Castleman disease with hyaline vascular morphology and lambda light chain predominance
EA4HP24-LYWS-369	Unicentric Castleman disease with atypical stromal spindle cell proliferation and indolent T-lymphoblasts in an HIV patient
EA4HP24-LYWS-381	Multicentric Castleman disease
EA4HP24-LYWS-385	Incidental, clinically silent early Kaposi sarcoma involving an isolated lymph node in an immunocompetent patient
EA4HP24-LYWS-390	Spectrum of IgG4 related disease in node: Castleman like follicular hyperplasia followed byclonal germinal centre proliferation
EA4HP24-LYWS-393	TAFRO/POEMS syndrome in a young patient with multicentric Castleman disease

EA4HP24-LYWS-397	Expanding the spectrum of KSHV/HHV8 disorder: Multicentric Castleman Disease associated with increase of IgG4 positive plasma cells.
EA4HP24-LYWS-402	Idiopathic multicentric Castleman disease (plasma cell type) with numerous IgG4 positive cells.
EA4HP24-LYWS-426	Castleman disease of hyaline-vascular type with extensive ossification
EA4HP24-LYWS-434	Thymic Castleman disease;IgG4 RelatedDisease
EA4HP24-LYWS-439	Idiopathic multicentric Castleman disease.
EA4HP24-LYWS-440	Lymphadenopathy with marked IgG4+ sheet-like plasma cells (favor IgG4-related LAD over plasma cell variant of Castleman disease)
EA4HP24-LYWS-446	HHV-8 associated multicentric Castleman disease
EA4HP24-LYWS-448	Castleman disease
EA4HP24-LYWS-452	HHV8-associated multicentric Castleman disease with plasmablastic aggregates
EA4HP24-LYWS-455	Hyaline vascular Castleman's disease with dysplastic follicular dendritic cells and loss of FDC markers

EA4HP24-LYWS-9

KSHV/HHV8-associated multicentric Castleman disease with fulminant clinical course

Prof. Stefan Dirnhofer

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Case Description

- Caucasian male, 35 years
- HIV - positiv
- Generalized lymphadenopathy, Hepatosplenomegaly
- Bicytopenia
- Fatigue, weight loss and myalgias
- Clinical question: Lymphoma? Infectious? Tumor?

Biopsy Fixation Details

Lymph node inguinal left, excisional biopsy, formalin - fixed, paraffin embedded

Frozen Tissue Available

no

Details of Microscopic Findings

Lymph node with altered structure: Follicles/germinal centers are atrophic and there is hypervascularity with many high endothelial venules; prominent peri- and interfollicular plasmacytosis with many plasmablasts in the mantle zone but also intrafollicular and perifollicular.

Immunophenotype

Few B- and T-cells (CD20 & CD3) in regular distribution; atrophic germinal centers are depleted of B-cells. The increased interfollicular plasma cells are polytypic and the plasmablasts but also plasmacytes are positive for LANA1. Very few, single EBV (EBER) positive cells. Most - if not all - HHV8-positive cells are EBV-negative

Cytogenetics

none

Molecular Studies

IgH - Rearrangement: polyclonal

TCR - Rearrangement: polyclonal

Proposed Diagnosis

KSHV/HHV8-associated multicentric Castleman disease

Interesting Feature(s)

Overlap of HHV8-associated MCD with KSV/HHV8-positive DLBCL, NOS

Fulminant clinical course (patient died due to multiorgan failure 4 weeks after dx)

EA4HP24-LYWS-10

Idiopathic multicentric Castleman disease-TAFRO syndrome

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Case Description

A 32-year-old male presented with several months of fatigue followed by two weeks of increasing abdominal swelling, shortness of breath, and 12 kg weight gain. Imaging studies showed large volume ascites, pericardial and bilateral pleural effusions, diffuse hypermetabolic lymphadenopathy, and splenomegaly. Laboratory studies were significant for thrombocytopenia (platelets 82 $x10^9$/L), elevated CRP (204 mg/L) and ESR (91 mm/h), and elevated alkaline phosphatase (1530 U/L). He was found to have renal failure requiring dialysis, and a renal biopsy showed features of thrombotic microangiopathy. Infectious and rheumatologic workups were unrevealing. A bone marrow biopsy showed slightly increased reticulin fibrosis (grade 1 of 3).

Biopsy Fixation Details

Excisional biopsy, left axillary lymph node, 10% buffered formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

Sections show overall intact lymph node architecture including uniformly small, well-spaced follicles. Germinal centers show moderate to marked regressive transformation, characterized by concentric layers of mantle zone lymphocytes which impart an "onion-skinning" appearance. Many germinal centers contain radially penetrating vessels, imparting a "lollipop" appearance. Rare follicles show multiple germinal centers within a single mantle zone (twinning). Moderately increased plasma cells within the interfollicular zone, follicular dendritic cell prominence, and increased vascular proliferation surrounding the regressed follicles are noted.

Immunophenotype

CD20-positive B-cells forming follicles are interspersed with CD3-positive T-cells predominantly in the interfollicular zone. Residual germinal centers are appropriately negative for BCL2. B-cells and plasma cells are polytypic by kappa and lambda light chains. HHV-8 stain is negative for viral inclusions. Cyclin D1 stains scattered histiocytes and is otherwise negative. KRT AE1/AE3 stain is negative.

Cytogenetics

Not performed

Molecular Studies

B-cell lymphoma, T-cell lymphoma, and plasma cell myeloma NGS panel, mutations identified (gene/allelic frequency):

SPEN/48%

KMT2D/48%
CUL4A/53%

Proposed Diagnosis

Castleman disease with mixed hyaline vascular and plasma cell features/idiopathic Multicentric Castleman disease-TAFRO syndrome (iMCD-TAFRO)

Interesting Feature(s)

TAFRO is a rare syndrome characterized by thrombocytopenia, anasarca, fever or hyperinflammatory status, reticulin fibrosis, renal insufficiency, and organomegaly. Even more rarely, patients with clinical features of TAFRO syndrome also display lymph node histopathology consistent with Castleman disease, as in our case, imparting a diagnosis of iMCD-TAFRO. Patients with iMCD-TAFRO are negative for other causes of MCD, including HHV-8. Interestingly, following this patient's lymph node excision, HHV-8 was detected by qualitative testing at an outside laboratory. However, subsequent quantitative testing for HHV-8 by real time PCR was negative. Recent studies have shown improvement in symptoms and outcomes in iMCD-TAFRO patients treated with anti-IL-6 therapy. Following this patient's diagnosis, treatment with siltuximab was initiated, with improvement in his thrombocytopenia, renal function and CRP elevation. He continues to require periodic large-volume paracentesis.

EA4HP24-LYWS-28

A strange "follicular lymphoma"

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Case Description

- 50 year-old man

- Fever and fatigue (during 1 month)
- Inflammatory biological syndrom
  CRP= 230, thrombopenia and anemia, LDH =450
  Polyclonal hypergammaglobulinemia
- **CT scan and FDG-scan**:
  Numerous enlarged lymph nodes (cervical, susclavicular, mediastinal, mesenteric, inguinal) SUVmax : from 3 to 6.5
  Splenomegaly and hepatomegaly
- No sign of infection (HIV negative)
- Bone marrow aspirate : presence of atypical « mature » cells

- **Lymph node surgical biopsy (axillary)** : referred for expertise (proposed diagnosis : follicular lymphoma)

Evolution :

A few days after the biopsy, the patient has been admitted in Intensive care unit due to sudden occurrence of serious respiratory, cardiac and renal failure.- Macrophage activation syndrom (HS score= 216)

- Elevated blood values of Triglycerids and ferritin

Slow recovery after treatment by Rituximab and etoposide

Biopsy Fixation Details

Formalin 4%

Frozen Tissue Available

no

Details of Microscopic Findings

Axillary Lymph node:

- The architecture is modified due to an exceedingly high number of follicles scattered throughout the lymph node. Some follicles are small or atrophic. The mantle zone is often enlarged. The intrafollicular content is relatively monomorphic, including a predominant component of medium/large sized cells with slightly irregular nuclei and occasional nucleoli.
- The sinuses are often enlarged and interfollicular areas are well-preserved.

Immunophenotype

- CD20 : weak and heterogeneous positivity within the follicles
- CD79A : predominant but heterogeneous positivity within the follicles
- BCL6 and CD10 : heterogeneous positivity within the follicles (globally weak)
- BCL2 : heterogeneous positivity within the follicles (globally weak)
- CD3 and CD5 : minor positivity (located between the follicles)
- CD138 : shows a few plasma cells outside the follicles
- Light chains : polytypic pattern outside the follicles.
- Monotypic Lambda positivity within the follicles- HHV8/ LANA: strong positivity within the follicles (plasmablasts), negative outsideEBER negative

Cytogenetics

ND

Molecular Studies

-Clonality analysis (BIOMED-2) : Node Biopsy :

Polyclonal pattern for IgH, IgK, TCR beta and TCR gamma genes.

Proposed Diagnosis

HHV8+ multicentric Castleman disease with atypical morphology, i.e.

Purely follicular plasmablastic proliferation mimicking Germinotropic Lymphoproliferative disorder (and to a lesser extent follicular lymphoma)

Interesting Feature(s)

Atypical morpho-phenotypic features (follicular proliferation) illustrating :

- the possibility of border-line lesions between HHV8+ MCD and HHV8+Germinotropic Lymphoproliferative disorder (due to the strong intrafollicular HHV8 positivity)<

- the possible confusion with follicular lymphoma (which was the initial diagnosis) in case of MCD with purely nodular CD10+/BCL2+ lesions, since HHV8 immunostaining is not always done in this setting.

-the importance of clinical information to interprete such lesions

EA4HP24-LYWS-48

A case of HHV-8 associated multicentric Castleman disease and multifocal Kaposi Sarcoma

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Case Description

·48 year-old man, originally from Kenya and residing in the US, who presented with fever, generalized weakness, and weight loss with recent history of travel to Kenya

·Transferred to ICU for subsequent salmonella bacteremia

·Found to have significant anemia and thrombocytopenia

·Imaging studies showed hepatosplenomegaly and lymphadenopathy above and below the diaphragmHgB: 7.1 g/dL, Hct: 21.7%, Plt: 83 x 103/L, WBC: 8.4 x 103/L

WBC differential unremarkable

Biopsy Fixation Details

·Excisional biopsy of right inguinal lymph node

—Dimensions: 1.5 x 1.0 x 1.0 cm

·Morphologic evaluation on a specimen fixed in formalin

·Flow cytometry was performed on a fresh fragment of tissue

Frozen Tissue Available

N/A

Details of Microscopic Findings

- Lymph node sections with widely spaced follicles, slightly expanded interfollicular areas, and foci of spindle cell proliferations
- Subset of follicles with atretic germinal centers
- Mantle zones with “onion skinning”
- Single penetrating sclerotic vessels
- Plasmablastic cells surrounding follicles and nodules
- Interfollicular areas with sheet-like plasmacytosis
- Medulla with slit-like vascular spaces and anastomosing vascular channels
- "Promontory sign” - newly formed vessels protruding into existing vascular space
- Parenchyma, capsule, and medulla with nodular areas composed of proliferating endothelial cells

Immunophenotype

IHC Antibodies	Pattern
CD3	T cells in interfollicular areas and scattered in germinal centers
CD20	B cells in follicles and scattered in interfollicular areas
CD21 & CD23	Follicular dendritic meshworks – including atretic subset
CD138	Increased plasma cells in interfollicular areas
Kappa and Lambda IHC	Lambda restricted plasmablastic cells surrounding nodules
CD30	Plasmablastic cells surrounding nodules and mantle zones
HHV-8	Plasmablastic cells surrounding nodules and mantle zones; spindle cells in nodules
ERG	Spindle cells in nodules
CD34	Spindle cells in nodules

Flow cytometry on lymph node:•Polytypic B cells
•No aberrant immunophenotype on T cells

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

HHV-8 associated multicentric Castleman Disease and concurrent multifocal Kaposi Sarcoma

Interesting Feature(s)

This is a rare and unusual case of an HIV negative and immunocompetent individual with:—Lymph node involvement by concurrent HHV8-positive MCD and KS
—Circulating plasmablastic cells in peripheral blood
—Fulfilling clinical and morphologic criteria for hemophagocytic lymphohistiocytosis
—Patient eventually succumbed to his disease due to multiorgan failure and hemophagocytic syndrome

MCD: Multi-centric Castleman Disease KS: Kaposi Sarcoma

EA4HP24-LYWS-53

A case of Castleman disease, plasmacytic variant, with cytogenetic clonal aberration

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Case Description·67 year-old woman who presented with chest pain and dyspnea
·Chest CT identified an enlarged supraclavicular lymph node (2.4 cm)
·HgB - 12.3 g/dL, Hct - 37%, Plt - 370 x 10^3/L, WBC 6.9 x 10^3/L
·WBC differential unremarkable·SPEP: 0.2g/dL M-spike Immunofixation: IgG, lambda light chain
·Two needle biopsies performed and showed plasma cells in sheets with lambda light chain restriction
·NGS: negative for BIRC3, CXCR, KLF2, and MYD88 mutations
·Insufficient tissue for B cell gene rearrangement studies
Differential diagnosis of needle biopsies: 1.Extraosseous plasmacytoma
2.Extraosseous infiltrate from plasma cell myeloma
3.Lymphoma with extreme plasma cell differentiation
·Excisional biopsy recommended
·Bone marrow biopsy obtained between needle biopsies and excisional biopsy: No evidence of systemic plasma cell dyscrasia

Biopsy Fixation Details
·Excisional biopsy of left supraclavicular lymph node
—Dimensions: 1.5 x 1.2 x 0.9 cm
·Morphologic evaluation on a specimen fixed in formalin
·Flow cytometry was performed on a fresh fragment of tissue, maintained in RPMI

Frozen Tissue Available
N/A

Details of Microscopic Findings
- Lymph node with distorted but overall preserved architecture
- Regressed or atretic germinal centers
- Follicles with single penetrating hyalinized vessel
- “Twinning of follicles”
- Interfollicular spaces (and paracortex) expanded with marked plasmacytosis
- Sheets of plasma cells with intermixed small polymorphous lymphocytes and histiocytes
- Mantle zones are well-defined and slightly expanded in some follicles
- Sinuses are patent

Immunophenotype

Marker	Pattern
CD3	T cells in interfollicular areas
CD20	B cells in follicles and rare forms in interfollicular areas
BCL-2	Mantle zone B cells (shows expansion in some follicles) and interfollicular T cells
CD138	Sheets of interfollicular and paracortical plasma cells
Kappa and Lambda IHC	Significant predominance of lambda light chain expressing plasma cells
CD21	Follicular dendritic meshworks – including atretic and regressed subset
HHV-8	Negative
EBER ISH	Negative

Flow cytometry:

Plasma cells highly skewed towards lambda light chain restriction (Lambda:Kappa ratio 8.5:1)

Cytogenetics

Loss of D13S319

Molecular Studies

N/A

Proposed Diagnosis

Reactive lymphadenopathy with extensive interfollicular plasmacytosis

Favor Castleman disease, plasmacytic variant

Interesting Feature(s)

This case was initially diagnostically challenging, given the prior inconclusive core needle biopsies that were suspicious for malignancy

- Excisional biopsy was consistent with Castleman disease, plasmacytic variant
  - Caveat that clonal abnormality was detected by FISH
  - Loss of D13S319 is a well-documented abnormality in several lymphoid and plasma cell disorders
    - Extraosseous involvement by a plasma cell neoplasm ruled unlikely given negative bone marrow biopsy, supporting reactive etiology in lymph node
- No specific or recurrent chromosomal translocations have been associated with unicentric Castleman disease
- Rare cases of Castleman disease with a clonal cytogenetic abnormality have been reported
  - Often hyaline-vascular variant cases
  - Only very rare cases of plasmacytic variant have been associated with clonal abnormalities

EA4HP24-LYWS-56

23-year-old man with idiopathic multicentric Castleman disease, NOS

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Case Description

A 23-year-old man presented with several months of intermittent fevers, night sweats, abdominal pain, nausea and lymphadenopathy (LAD) and reported significant fluid retention, gaining 60 lb. over the previous month despite treatment with furosemide. Generalized edema was noted. Imaging showed periportal edema, splenomegaly (15.4 cm), retroperitoneal pelvic inguinal LAD, hypermetabolic cervical, axillary, and mediastinal lymph nodes (LN), pleural effusions, and anasarca. He was HIV and heterophile antibody negative but EBV positive (viral load 1600 copies/mL). Peripheral blood (PB) flow cytometry was negative for lymphoma. A bone marrow (BM) biopsy was unremarkable. CBC showed WBC 13 K/µL, Hgb 7.6 g/dL, MCV 85 fL, and plt 210 K/µL. Additional labs showed elevated CRP (8.2 mg/dL), abnormal renal function (BUN 86 mg/dL, creatinine 4.3 mg/dL, decreased GFR), hypoalbuminemia (2.9 g/dL), and kappa Bence Jones proteinuria. Serum IL-10, IL-2R, IL-6, and VEGF were elevated.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

None

Details of Microscopic Findings

The interfollicular areas of the axillary LNs were variably expanded by a mixed cell population. Focal dermatopathic change was seen. Areas with many prominent plasma cells forming sheets were present. Germinal centers (GC) showed variable morphology but contained a mixed cell population. Many GCs were regressed and lymphocyte-poor, surrounded by concentric rings of small lymphocytes penetrated by perpendicular vessels. The prominent vasculature was often lined by plump endothelial cells.

Immunophenotype

Flow cytometry showed polytypic CD19, CD20+ B cells without a significant number of CD10+ B cells. T cells expressed all pan T cell antigens with a CD4:CD8 ratio of 1.3:1. Immunostaining showed CD20, PAX5+ B cells and CD3, CD2+ T cells with many polytypic plasma cells. No LANA+ (KSHV/HHV-8) cells were seen. There was a very small number of scattered variably sized EBV+ (EBER probe) cells.

Cytogenetics

Cytogenetic analysis showed a normal karyotype.

Molecular Studies

PCR gene rearrangement analysis showed polyclonal patterns for TCR gamma chain, IgH chain, and IgK light chain genes. NGS detected variants of unknown significance for *ATM* (c.610G>A, 50% VAF) and *BRCA1* (c.341C>G, 51% VAF).

Proposed Diagnosis

Idiopathic multicentric Castleman disease, NOS

Interesting Feature(s)

This is a case of idiopathic multicentric Castleman disease (iMCD), NOS in a young HIV-negative man who presented with generalized LAD, splenomegaly, constitutional symptoms, severe anemia, anasarca, pleural effusions, hypoalbuminemia, and renal dysfunction. LN biopsy showed prominent polytypic plasmacytosis, prominent vascular proliferation, dermatopathic lymphadenitis, and regressed GCs surrounded by concentric rings of small lymphocytes penetrated by perpendicular vessels. Serum IL-10, IL-2R, IL-6, and VEGF were elevated suggestive of cytokine storm. This patient showed 4 of 5 features of the TAFRO form of iMCD: (A) anasarca, (F) fever/hyperinflammatory state, (O) organomegaly (LAD, splenomegaly), and (R) renal insufficiency; however, his platelet count (T for thrombocytopenia) was normal. The presence of a monoclonal protein in the urine raised the suspicion of POEMS. However, the BM biopsy showed no monoclonal plasma cell population or evidence of neuropathy. Thus, this patient is best classified as iMCD, NOS, although exhibiting 4 of 5 features of TAFRO.

EA4HP24-LYWS-62

Follicular lymphoma with hyaline-vascular Castleman-like features.

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Case Description

A 70-year-old male patient with an umbilical hernia surgery. Three months after the procediment, he complained about weight loss, anorexia and abdominal pain.

On physical examination, the patient presented with poor general condition and distended abdomen.

Palpable adenopathy of 2 cm was evident in the right inguinal region, with pathological findings on ultrasound.

In PET-scan, multiple retroperitoneal lymphadenopathies were identified with a mesenteric lymph node measuring 46 x 7 mm. Furthermore, bone marrow reactivity was presented.

An excision biopsy of an inguinal lymphadenopathy was performed.

Biopsy Fixation Details

Nodular tissue of elastic consistency measuring 2.5 x 2 x 1 cm maximum diameters

Frozen Tissue Available

No Frozen Tissue

Details of Microscopic Findings

Microscopically, the lymph node architecture was altered. There were numerous regressed germinal centers surrounded by expanded mantle zones forming concentric rings with an "onion skin" pattern.

Marked proliferation of high endothelial venules penetrating the germinal centers and the interfollicular zone, were presented.

Likewise, few follicles were large, with centrocytes and less than 15 centroblasts per high-power field were observed.

Immunophenotype

The neoplastic cells were CD20, BCL2, BCL6 and LMO2 positive, with an index of proliferation of 30%. CD10 was negative. CD21 showed expanded and also regressed pattern of follicular dendritic cell meshworks. No Kappa/Lambda light chain restriction was identified. Herpes 8 and EBER were negative.

Cytogenetics

BCL2 and *BCL6* were rearranged by fluorescence in situ hybridization study.

Molecular Studies

NGS showed a pathogenic variant of the *CXCR4* gene and probable pathogenic variants of the *KMT2D* and *CARD11* genes.

Proposed Diagnosis

FOLLICULAR LYMPHOMA GRADE 1-2, WITH HYALINE-VASCULAR CASTLEMAN-LIKE FEATURES.

Interesting Feature(s)

Castleman disease (CD) is a diagnosis of exclusion where lymphomas must be rule out.

Follicular lymphoma (FL) with hyaline-vascular CD-like features is an uncommon variant which may create diagnostic challenges especially in small biopsies where neoplastic follicles may be absent and CD changes can dominate the histology.

It is important to differentiate both diseases given the differences in treatment and prognosis of patients with each disease.

Nowadays, there are cases of FL with double positive *BLC2* and *BCL6* rearrangements; BCL6 is a transcriptional repressor which plays a role in the formation of the germinal center and also is involved in B-cell lymphomagenesis.

KMT2D is a histone and chromatin-modifying gene most frequently mutated in FL (80-90%).

CARD11 promotes *NF-κB* activation upon antigen receptor ligation in B-cells and is mutated in 10% of FL cases.

CXCR4 has a role in cell migration to lymph nodes and bone marrow, less frequently mutated in FL.

EA4HP24-LYWS-68

HIV-associated HHV8-positive multicentric Castleman disease with concurrent Kaposi sarcoma

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Case Description

A 41-year-old male with HIV/AIDS presented with pancytopenia, very low CD4 count, worsening constitutional symptoms, significant lymphadenopathy and clinical/laboratory findings consistent with hemophagocytic lymphohistiocytosis (HLH). A left inguinal lymph node excisional biopsy was performed.

Biopsy Fixation Details

Left inguinal lymph node excisional biopsy; fixed in 10% neutral buffer formalin

Frozen Tissue Available

Not applicable

Details of Microscopic Findings

Sections of the left inguinal lymph node excisional biopsy show fragments of lymphoid tissue with few vaguely nodular aggregates of small-to-medium mature lymphocytes admixed with few atypical variably-sized immunoblast/plasmablast-like cells. Vascular proliferation is noted. Mitotic figures are evident. No definitive follicles are identified. No cells with Hodgkin/Reed-Sternberg morphology, necrosis or viral inclusions are present. Additionally, focally distinct and interspersed collections of spindle cells are evident with minimal atypia showing elongated nuclear contours, dispersed chromatin, inconspicuous nucleoli and pale cytoplasm arranged in focally curved fascicles separated by slit-like vascular spaces with extravasated red blood cells. Many hyaline globules and hemosiderin deposits are noted.

Immunophenotype

HHV8 is positive (nuclear dot-like/speckled staining pattern) in the spindle cell population that is also positive for CD34 and CD31; and is negative for CD68, ALK1 and EBER in-situ hybridization. PAS shows many intra/extracellular hyaline globules.

Embedded within the B-cell aggregates, many scattered variably-sized HHV8-positive cells (distinct from the HHV8-positive spindle cell population) are evident without clusters/sheets. These HHV8-positive cells are IgM-lambda restricted; positive for MUM1 and C-MYC (weak/variable); and are negative for CD138, CD30, IgG and EBER in-situ hybridization. CD138 and MUM1 highlight inter-nodular clusters/sheets of polyclonal (kappa and lambda) plasma cells; negative for IgM. EBER in-situ hybridization highlights few scattered cells (focally up to 40/HPF), distinct from the HHV8-positive cells.

CD20 highlights few vaguely nodular aggregates of small-to-medium B-cells that are also positive for CD79a, BCL2 (strong), IgD (subset) and IgM (few/focal; weak), consistent with a mantle-cell phenotype; CD21 weakly stains the associated residual follicular meshwork. Ki-67 shows an overall moderate proliferative fraction. CD30 stains rare para-nodular and

scattered immunoblasts. CD3 stains interspersed reactive T-cells; CD4 and CD8 stain a subset of T-cells (CD4 <<< CD8). No atypia of the T-cells is evident. CD4 and CD68 highlight few scattered histiocytes. CD34/CD31 additionally highlights vasculature. TdT stains rare scattered positive cells. CMV is negative for viral elements. Special stains AFB and GMS are negative for acid fast bacilli and fungal elements, respectively.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

HIV-associated HHV8-positive multicentric Castleman disease with concurrent Kaposi sarcoma

Interesting Feature(s)

HIV-associated HHV8-positive multicentric Castleman disease with concurrent Kaposi sarcoma

EA4HP24-LYWS-71

Idiopathic Multicentric Castleman Disease, HHV8-Negative, With Increased IgG4-Positive Plasma Cells

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Case Description

52 year old man presented with left axillary lymphadenopathy and anemia following COVID infection. Imaging showed enlarging left axillary lymphadenopathy (up to 4.1 cm to 6.2 cm over 6 months). PET scan confirmed localized axillary disease. Inflammatory markers progressively increased (ESR up to >145 mm/hr, CRP up to 408.6 mg/L) with positive ANA (1:160 and speckled). Serum proteins showed increased IgG4 (up to 623 mg/dL) and SPEP was polyclonal. IL-6 was also increased (121.6 pg/mL). Extensive infectious workup was negative. A left axillary lymph node dissection nine months later revealed classic Hodgkin lymphoma. He received six cycles of Bv-AVD with complete resolution of disease, but with new cervical lymphadenopathy (right greater than left).

Biopsy Fixation Details

Initial (7/1/22): Left deep axillary lymph node excision measuring up to 5.6 cm fixed in formalin.

CHL (3/16/23): Left axillary lymph node excision measuring up to 6.1 cm fixed in formalin.

Follow-up (10/27/23): Right levels 2 and 3 lymph node excisions measuring up to 2.0 cm fixed in formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Initial (7/1/22): Enlarged lymph node with thickened capsule remarkable for follicular and paracortical hyperplasia with numerous interfollicular plasma cells. Occasional atrophic follicles and onion-skinning of mantle zones are also seen.

CHL (3/16/23): Enlarged lymph node with thickened capsule and hyalinized vessels with a mixed polymorphous infiltrate including large, atypical HRS-like cells arising in a background of Castleman disease.

Follow-up (10/27/23): Similar to initial biopsy with more prominent hypervasularity and without HRS-like cells.

Immunophenotype

Initial (7/1/22): CD138, IgG and IgG4 show polyclonal plasmacytosis with greater than 40% positive for IgG4 (up to >100/HPF). HHV8, EBV and treponema are negative. Flow cytometry shows polytypic B cells and CD4-skewed T cells (CD4:CD8 = 3.9).

CHL (3/16/23): The HRS-like cells are positive for PAX5, MUM1, CD30 and CD15 (subset), while negative for CD3, CD20, CD45 and ALK1. HHV8 and EBV are negative. CD138, kappa, lambda, IgG and IgG4 show polyclonal plasmacytosis with 40% positive for IgG4 (up to >100/HPF). Flow cytometry was not performed.

Follow-up (10/27/23): CD138, kappa, lambda, IgG and IgG4 show polyclonal plasmacytosis with 30% positive for IgG4 (up to >100/HPF). Scattered immunoblasts are highlighted with CD20, PAX5, MUM1 and CD30, and are negative with CD15. HHV8 and EBV are negative. Flow cytometry shows polytypic B cells and CD4-skewed T cells (CD4:CD8 = 8.3).

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Idiopathic multicentric Castleman disease, HHV8-negative

Interesting Feature(s)

IgG4-related disease can show a spectrum of patterns, including Castleman disease-like, and multicentric disease can show increased IgG4-positive plasma cells, overlapping the diagnostic features. However, IgG4-related disease requires the exclusion of other entities, including Castleman disease. IL-6 was significantly increased, likely contributing to the robust IgG4 plasmacytosis. This case showed the evolution of iMCD initially mimicking IgG4-related disease to fully manifested iMCD with progressively increased inflammatory markers, multicentric lymphadenopathy and persistent anemia without infection, autoimmune disease or prior malignancy. Histologic findings also continued to be consistent with iMCD, including regressed and hyperplastic germinal centers, plasmacytosis and hypervascularity. iMCD also increases the risk of lymphomas, such as CHL, which this patient also developed.

EA4HP24-LYWS-78

HHV-8-associated Multicentric Castleman Disease and Kaposi Sarcoma in a 70-year-old HIV-negative man

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Case Description

A 70-year old man presented with symptoms suggestive of metabolic encephalopathy. His past medical history was only significant for gout, chronic kidney disease and hypertension. No fever, chills, headache, vision change, rash, gastrointestinal or genitourinary symptoms were present on physical exam. Computed tomography scan showed diffuse lymphadenopathy. Brain magnetic resonance imaging showed stable gliosis in the occipital periventricular white matter and loss of the normal fatty marrow signal. Workup for HIV1/2 and Hepatitis were negative. A bone marrow biopsy and a cervical lymph node excision were performed.

Biopsy Fixation Details

Lymph nodes were fixed in formalin except for what was preserved for flow cytometry. The bone marrow biopsy was placed in Bouin's fixative.

Frozen Tissue Available

None

Details of Microscopic Findings

The lymph node architecture is relatively preserved with Interfollicular areas showing prominent hyperplasia consisting of plasma cells. Many atrophic follicles are present, which contain scattered and small clusters of plasmablastic cells in the mantle zones. These plasmablasts range in size from medium to large with one to two nucleoli with moderate amount of amphophilic cytoplasm. There is also a paracortical focus of vascular proliferation with spindle-shaped slit-like vascular channels containing erythrocytes.

Immunophenotype

The atrophic follicles were highlighted by CD21 and CD23, with scattered BCL6 positive cells, which showed to be mostly replaced by plasmablasts (positive for MUM-1, OCT-2, BOB-1, c-MYC (subset) and negative for CD10, CD20, CD79a, PAX5, CD138, BCL6, BCL2, CD30, EBER).

The plasma cells were positive for CD138, MUM-1, weak CD79a and negative for CD56, cyclinD1. KISH and LISH staining appeared to be polytypic, though LISH stain was suboptimal. EBER-positive cells are very rare.Ki-67 proliferation index was approximately 50% overall.

In an area with atypical vascular proliferation, the plasmablasts were positive for MUM-1, IgM, HHV-8, lambda and negative for CD138, kappa, with higher ki-67 proliferation index

(approximately 70%). CD21 and CD23 highlighted atrophic follicular dendritic meshwork. The spindle cells in the focal vascular area were positive for HHV-8 as well.

Cytogenetics

None performed

Molecular Studies

IgH and IgK gene status were negative. T-cell receptor gamma rearrangement was negative.

Proposed Diagnosis

HHV-8-associated lymphoproliferative disorder consistent with multicentric Castleman's disease.

Interesting Feature(s)

There were two interesting features in the present case:

- The condition arose in a patient with absent HIV1/2 infection or other immunocompromising conditions.
- A focus of atypical vascular proliferation revealed the presence Kaposi sarcoma.

Although not unique, these findings highlight the diverse clinical and morphologic spectrum of Castleman's disease.

EA4HP24-LYWS-82

Splenic involvement in HHV8-related multicentric Castleman Disease.

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Case Description

A 65-year-old male was hospitalized for a fever of unknown origin. PET-CT scan highlighted 13 cm splenomegaly and multiple hypercaptating lymphadenopathies above and below the diaphragm.

Blood count results were the following: Hb 7,6 g/dL, WBC 1500/mm3, PLT 50.000/mm3. Systemic infection and autoimmune disorders were excluded a the laboratory investigations. Bone marrow biopsy was negative for neoplasia. Empiric intravenous immunoglobulins and systemic steroids were started but were ineffective.

A year after the presentation, due to a worsening of the splenomegaly, a lymphoproliferative disorder was suspected. The patient underwent a diagnostic splenectomy, resulting in a diagnosis of HHV8-related MCD.

After splenectomy, blood counts improved as well as the lymphadenopathies. The patient is current in complete remission, 20 months after the diagnosis.

Biopsy Fixation Details
FFPE
Frozen Tissue Available
No
Details of Microscopic Findings
At splenectomy, white pulp follicles were numerous but exhibited varying degrees of regression and atrophy with multiple "onion-bulb" figures. CD23 immunostaining highlighted an increased follicular dendritic cell meshwork within regressed germinal centers. The red pulp was congested and was occupied by an abundant population of slightly atypical CD138+ plasma cells in aggregates, lymphocytes, and lipofuscin-like pigment-storing histiocytes. HHV8 immunostaining was positive in intra- and inter-follicular lymphocytes. A focal subcapsular D2-40+ vascular proliferation also stained for HHV8 leading to a diagnosis of an associated Kaposi sarcoma.
Immunophenotype
N/A
Cytogenetics
N/A
Molecular Studies
N/A
Proposed Diagnosis
Splenic localization of HHV8-related multicentric Castleman disease.
Interesting Feature(s)
The splenic involvement in Castleman disease is extremely rare, mostly limited to the multicentric variant. Such cases may clinically mimic a lymphoproliferative neoplasm, and splenectomy has therefore an important role in the diagnosis of these patients.

EA4HP24-LYWS-99

Diagnostic Mimic of Multicentric Castleman Disease in a Lymph Node of a 76-year-old woman with Schnitzler Syndrome

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Case Description
The patient is a 76-year-old woman with a history of hypothyroidism who presented with recurrent fevers, urticarial skin lesions and IgM monoclonal gammopathy, and diagnosed with Schnitzler syndrome (SS) in 2014. She has had stable bilateral inguinal and axillary lymphadenopathy. An excisional biopsy of the left inguinal lymph node (LN) was performed in September, 2023 to evaluate for possible lymphoproliferative disorder (LPD).

Biopsy Fixation Details

The excisional lymph node biopsy was fixed in 10% neutral buffered formalin solution overnight.

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections show lymph nodes with preserved architecture. Patent sinuses filled with histiocytes and nodular paracortical hyperplasia are seen. Follicles are slightly increased. They harbor germinal centers, ranging from regressed to moderately hyperplastic. Focal hyalinization is seen within many germinal centers with mild prominence of follicular dendritic cells. Mantle zones are frequently expanded, with occasional appearance of onion-skin layering. There is increased vascularity, with increased, prominent high endothelial venules in the interfollicular area and occasional vessels penetrating into germinal centers (lollipop lesions). Plasma cells are moderately to markedly increased. In summary, the histologic sections of the lymph node exhibited morphologic features resembling those seen in multicentric Castleman disease (MCD).

Immunophenotype

CD20 and PAX5 highlight B-cells present in follicles as well as scattered in the interfollicular area. CD3, CD5 and CD43 highlight T cells present predominantly in the interfollicular regions. BCL6 and CD10 highlight germinal centers, some of which appear small and atrophic. BCL2 is appropriately negative in the germinal centers (GC) Cyclin D1 and CD43 are negative in the B-cells. CD138, MUM1 and CD43 highlight many interfollicular plasma cells (PC) which are mostly positive for IgM. The PC demonstrate kappa light chain predominance. IgG4 stains about 5% of the plasma cells. Ki-67 is appropriately high in the GC and low (5%) elsewhere. HHV-8 is negative.

Cytogenetics

Normal Female Karyotype

Molecular Studies

IGH and IGK gene rearrangement analyses demonstrated clonal rearrangements. NGS mutation profiling identified MYD88 L265P mutation at a variant allele frequency of 8.1%.

Proposed Diagnosis

Lymph node with Castleman-like features and clonal IgM plasmacytosis, consistent with the clinical diagnosis of Schnitzler syndrome

Interesting Feature(s)

To our knowledge, this is the first case to include comprehensive morphologic, immunophenotypic and molecular characterization of a LN in a patient with SS. LN in SS can morphologically mimic MCD, and should be included in the differential diagnoses. LN associated with SS can be distinguished from MCD by immunophenotypic studies as well as clinical correlation. While the former shows predominance of IgM+ PC with skewed light chain expressions, PC in MCD are usually IgG+ and polytypic. In addition, MYD88 L265P mutation is unusual for MCD but has been reported in 45% of patients with SS. It demonstrates a possible pathogenic link among the atypical plasmacytic proliferation seen in SS, IgM MGUS, NOS, and lymphoplasmacytic lymphoma (LPL). While no monotypic

lymphocytes are identified in LN in SS, IgM MGUS, NOS and LPL consist of clonal B-cells and plasma cells. The question whether SS is a smoldering LPD remains open.

EA4HP24-LYWS-106

IgG4-related lymphadenopathy mimicking Casteman Disease, hyaline vascular variant

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Case Description

A 49-year-old male with a history of iron deficiency anemia and an ascending aortic aneurysm presented for evaluation of an abdominal mass.

CT imaging of the abdomen and pelvis was notable for a 4.2 cm contrast-enhancing mesenteric mass just left of the midline, contiguous with the adjacent bowel.

A PET-dotatate scan revealed a hypermetabolic mesenteric mass with likely involvement of the adjacent small bowel loop to the left of the midline with SUV max of 10.9 (measuring approximately 4.5 x 3.4 cm), consistent with a neuroendocrine tumor with adjacent satellite hypermetabolic mesenteric lymph nodes.

He subsequently underwent an exploratory laparotomy with small bowel and mesenteric mass resection.

Biopsy Fixation Details

The excisional specimen was fixed in 10% buffered formalin and slides of 4-6 µm sections were cut from formalin-fixed paraffin embedded tissues.

Sections were stained with hematoxylin and eosin and immunohistochemistry was performed using standard procedures.

Frozen Tissue Available

Not Applicable

Details of Microscopic Findings

Serial sections of the small bowel with mesenteric mass and adjacent lymph node revealed a broad morphologic spectrum, including prominent follicular hyperplasia, progressive transformation of germinal centers, focal Castleman "like"-changes in follicles and interfollicular expansion of numerous reactive plasma cells.

Immunophenotype

The expanded plasma cells population was noted to be polytypic for kappa and lambda expression by in situ hybridization. IgG4 staining highlighted >100 plasma cells per high power field, with an IgG4:IgG ratio >40%.

CD3 and CD20 highlighted T-cell and B-cells in adequate compartments, respectively.

BCL6 highlighted reactive germinal centers that were negative for BCL2 expression. CD5 highlighted T-cells and Cyclin D1 was negative in lymphocytes.

Cytogenetics

Not applicable

Molecular Studies

Not applicable

Proposed Diagnosis

The findings were supportive of IgG4-related lymphadenopathy. The patient was subsequently found to have elevated serum IgG4 (202 mg/dL).

Interesting Feature(s)

The patient was thought to have a neuroendocrine tumor based on his hypermetabolic PET- scan.

The morphologic findings greatly mimicked Castleman Disease, hyaline vascular. However, the characteristic spectrum of pathologic findings in addition to the raised serum IgG4 levels are all in favor of IgG4-related lymphadenopathy.

EA4HP24-LYWS-111

HHV-8 Positive Multicentric Castleman Disease Presenting with Hemophagocytic Lymphohistiocytosis

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Case Description

A 62-year-old man was admitted for fever of unknown origin for 9 months. The patient had traveled to Haiti prior and was treated for malaise. Later he got covid infection twice and developed night sweats, weight loss, and fevers. CT scan of the abdomen pelvis showed splenomegaly, extensive abdominal and pelvic lymphadenopathy. The patient was admitted to an outside hospital where he underwent extensive work-up which included lymph node biopsy, liver biopsy, colonoscopy, and infectious diseases, which were all negative. The patient was treated with doxycycline and steroid, but the fever persisted. After transferred to our facility, the patient underwent bone marrow biopsy due to anemia, thrombocytopenia, and splenomegaly. Relevant lab results: Ferritin 1326 ng/mL; Fibrinogen 413 mg/dL; Soluable IL-2 > 26K; EBV DNA 1100 IU/mL; IL-6 50 pg/mL. Triglyceride was not available.

The patient was treated with rituximab and etoposide and is currently on rituximab maintenance therapy. Now, patient does not have any hematologic related complaint.

Biopsy Fixation Details

The bone marrow aspirate smears were stained with Diff-Quik stain. The bone marrow core biopsy was submitted in formalin and processed after decalcification using

The lymph node biopsy was submitted for lymphoma work up. A portion of the tissue was sent for flow cytometry analysis and the remaining tissue was fixed in formalin and processed.

Frozen Tissue Available

NA

Details of Microscopic Findings

The bone marrow biopsy showed hypercellular marrow with granulocytic predominance and marked polytypic plasmacytosis. Scattered hemophagocytic histiocytes are noted. There were increased plasma cells.

Due to diffuse lymphadenopathy, subsequently, a lymph node biopsy was performed to establish the cause of HLH. The lymph node showed effacemnet of architecture by sheets of polytypic plasma cells and hypervascularity. Typical Castleman disease morphology such as regressed germinal center, FDC predominance, hypervascularity, or hyperplastic germinal centers, was not evident. .

Immunophenotype

CD20 showed the reminent of the lymphoid aggregates which were disrupted by sheeet of polytypic plasma cells. Immunohistochemical stain for HHV8 showed clusters of positive cells. The findings are most consistent with HHV8 positive multicentric Castleman disease with associated hemophagocyti lymphohistiocytosis.

Cytogenetics

Not available

Molecular Studies

Not available

Proposed Diagnosis

HHV-8 Positive Multicentric Castleman Disease Associated with secondaru hemophagocytic lymphohistiocytosis

Interesting Feature(s)

This was a case of a non-HIV patient who developed the disease after Covid infections, likely due to post infection immunosuppression. Clinical features were non-specific but need to have high awareness. Diagnosis of HLH was made in the bone marrow biopsy but the etiology should be established, whether this was primary or secondary, the latter is more common in adult population. The prescence of polytypic plasmacytosis in the bone marrow could be seen in viral infection but the subsequent lymph node biopsy helped to establish the etiology.

The initial core biopsy was done and showed polytypicl plasmacytosis with HHV8. Later an excisional biopsy was performed to better evaluate the architecture. The lymph node architecture was entirely effaced by sheets of plasm cells without decernable lymphoid follicles. The typical Castleman disease morphology such as germinal center hyperplasia or FDC hyperplasia/vacularity was not present. It is important to maintaine high level of suspicion to perform HHV-8 study even in the absence of typical morphology.

EA4HP24-LYWS-114

Castleman disease (iMCD?) with follicular neoplasia in situ in the setting of long lasting SAPHO syndrome

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Case Description

Now66-yrs-old lady was admitted at the Institute of Oncology Ljubljana for the first time in 1999. at the age of 41 after excision of the non-ossifying fibroma of the maxilla. In 1990. she underwent surgery for discus hernia, was suffering from frequent episodes of sciatica and diffuse vertebral pain. Skeletal scintigraphy showed multiple changes of osteosclerotic ans osteolytic type in axial skeleton and both iliacal bones being suspitious for metastases. Multiple bone biopsies were performed in the period of a few months not showing neoplastic pathology, just thickened bone trabecules. As well, immaging procedures showed no progression of bone changes. She has been suffering from acne as well. Her laboratory results were unremarkable including all tumor markers. In 2004 she was lost for our follow up, coming back in 2016. with the diagnosis of SAPHO syndrome which was delivered by endocrinologist in 2004. In 2016. she underwent surgery for well-differentiated T1c N0 right breast carcinoma being additionally treated with radiotherapy and Nolvadex. Again, in 2020 excision of T1c N1a well-differentiated left breast carcinoma was performed with subseqent axillar dissection which showed hialino-vascular Castleman disease in axillary lymph nodes with focally present FNis. She underwent RT again and was administred Nolvadex for 5 years. In 2021. enlarged right neck lymph node was excised with CD-HV again with focal presence of FNis. There are mildly elevated creatinine levels (86) as well as LDH (4.22), other laboratory results are normal (SR, CRP, Hb, Plts, albumins). There are no data about existence of polyclonal hypergamaglobulinemia. She is suffering from extreme fatigue and night sweating, having no fever or weight loss.

Her sister have been treated for breast carcinoma at age of 34 and was diagnosed with unicentric Castleman disease in the age of 31.

Biopsy Fixation Details

10% buffered formaline

Frozen Tissue Available

no

Details of Microscopic Findings

Morphological changes in line with the hyalino-vascular type of Castleman disease with increased intesity of bcl-2 staining within some germinal centers being CD10 positive as well.

Immunophenotype

CD20/CD10/bcl-6/bcl-2 positive germinal center cells.

Cytogenetics

NA

Molecular Studies

FISH for bcl2 translocation positive in germinal centers.

NGS (TruSight Oncology 500) and fusionPlex Lymphoma Kit: No clinically significant mutations identified. Class III mutation in ERBB2 (VAF 49.9), HOXB13 (VAF 49.18), TRAF2 (VAF 46), TSC2 (VAF46.36).

Proposed Diagnosis

CD with FNis in patient with long lasting SAPHO Syndrome. iMCD? (2 major criteria, 1 minor criteria - clinical).

Interesting Feature(s)

1. This is a first case of CD (iMCD?) reported in patient with SAPHO syndrome. Development of CD in the background of long-lasting SAPHO syndrome - SAPHO syndrome is characterized by increased levels of IL-6.
2. Overlapping systemic symptoms of fatigue, night sweating and bone pain overlap in SAPHO syndrome and due to the therapy with Nolvadex, blurring the systemic symtoms of iMCD (minor criteria!).
3. Questionable familial clustering of CD? Patient's sister was diagnosed with CD.
4. FNis in CD. There are a few case reports about FL with CD-like featureas. They could represent FL that arised in the setting of long lasting, unrecognized CD.

EA4HP24-LYWS-118

EBER and HHV8 (+) high grade B cell lymphoma with multicentric Castleman like features arising in the setting of immunodeficiency

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Case Description

49 year old, HIV positive, male patient. Presented with high fever (380C), loss of appetite, fatigue, weight loss (24 kg). Laboratory findings: Hb: 7,5 g/dL, Plt: 49.000 µL, WBC: 1770 µL, sedimentation rate: 97 mm/hr, CRP: 31 mg/dL. Imaging: PET-CT: Multiple enlarged lymph nodes in supra and infradiaphragmatic stations, measuring between 1cm to 1,9cm (SUVmax: 13,7 - 37,7)

Biopsy Fixation Details

Consultation of left cervical lymph node excision. The specimen was fixed in 4% formaline.

Frozen Tissue Available

None

Details of Microscopic Findings

The lymph node architecture was partially effaced by diffuse & vagually nodular infiltration. In focal areas small follicules with Castleman like changes, containing immunoblastic cells in mantle zone. There were numerous plasma cells in the interfollicular area. Diffuse & vagually nodular infiltration areas composed of cells with immunoblastic features. There were also areas involved by diffuse infiltration of immunoblastic/plasmablastic cells with starry sky appearance.

Immunophenotype

Infiltration was (+) with CD20, MUM1,CD38, λ, IgM, HHV8, EBER,CD30, cMYC and (-) with CD138, K, IgG, IgA, IgD, CD10, BCL6, PAX5, EBV-LMP, CD3. Plasma cells were politypic for K and λ light chain in Castleman like areas.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

EBER and HHV8 (+), high grade B cell lymphoma with multicentric Castleman like features, arising in the setting of immunodeficiency (HIV+). Differential diagnosis includes extra cavitary primary effusion lymphoma and EBER (+), HHV8 (+) diffuse large B cell lymphoma

Interesting Feature(s)

Striking diversity of morphologic and immunophenotypic features nearly encompasing all of the plasmablastic/immunoblastic lymphoproliferative disorders with EBV / HHV8 positivity.

EA4HP24-LYWS-128

HHV8+ plasma cell variant of Castleman disease with concurrent Kaposi sarcoma

Dr. Arpan Samaddar, **Dr. Rebecca L. King**

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Case Description

A 25-year-old man presented with fever, splenomegaly, multicentric lymphadenopathy and pancytopenia. He underwent excisional biopsy of a right inguinal lymph node. He was known to be positive for HIV.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

NA

Details of Microscopic Findings

Sections of the lymph node show architectural effacement of the lymph node with a subcapsular spindle cell proliferation extending into the parenchyma. In addition, the lymphoid parenchyma is distorted with several small, regressed germinal centers that show follicular dendritic cell prominence and occasionally rimming of mantle zone lymphocytes. Of note, there are scattered intermediate to large-sized cells compatible with plasmablasts in the periphery of these follicles and colonizing the regressed germinal centers. The interfollicular area is expanded with sheets of mature plasma cells.

Immunophenotype

CD138 highlights the expansion of interfollicular plasma cells in a sheet-like manner. These plasma cells are polytypic with kappa and lambda staining. In contrast the CD138 negative plasmablasts which are localized both within and around the follicles are cytoplasmic lambda light chain-restricted and positive for HHV8. The spindle cell proliferation is positive for HHV8 and ERG. EBV is positive in numerous scattered cells predominantly in an interfollicular distribution, distinct from the HHV8-positive cells. CD20 positive B cells are mainly localized in the residual follicles with a few scattered in the interfollicular areas.

Cytogenetics

NA

Molecular Studies

NA

Proposed Diagnosis

1. Castleman disease, plasma cell variant, HHV8/KSHV positive
2. Kaposi sarcoma
3. EBV reactivation/nondestructive EBV lymphoproliferative disorder secondary to immune suppression.

Interesting Feature(s)

Castleman disease (CD) is histologically classified as hyaline vascular (HV) type and the plasma cell (PC) type. Most PC cases correspond with multicentric disease clinically. Of multicentric CD, the HHV8/KSHV+ cases represent a distinct clinicopathologic entity typically occurring in patients with HIV. Our case shows the typical morphologic and phenotypic features of HHV8+ PCCD. Histologically, HHV8+ CD is characterized by relatively preserved lymph node architecture with interfollicular polytypic plasmacytosis. Regressed hyalinized follicles, lymphodepletion and interfollicular vascular proliferation may be seen. HHV8/KSHV infected medium to large plasmablasts are commonly identified in the mantle zones and have been reported to be polyclonal with respect to immunoglobulin gene rearrangement but will show lambda light chain restriction.[1,2,3,4] These plasmablasts may form small aggregates, as in our case. In some cases these may progress to HHV8+ diffuse large B cell lymphoma.[5] Patients with HHV8/KHSV associated multicentric CD commonly have concurrent Kaposi sarcoma, particularly those with HIV. In this case, Kaposi sarcoma was present in the same lymph node. In addition, in keeping with the patient's immune

suppression, there were numerous EBV positive cells in an interfollicular distribution, distinct from the HHV8-positive cells representing EBV reactivation/non-destructive EBV-associated B cell lymphoproliferative disorder.

EA4HP24-LYWS-141

Paraneoplastic Castleman disease like histopathological features in plasma cell neoplasia/POEMS syndrome.

Laura Rodriguez Merino, **Prof. Santiago Montes Moreno**

Hospital Universitario Marques de Valdecilla, Anatomic Pathology, Santander, Spain

Case Description

We report a case of a 66-year-old woman with multiple lymphadenopathies, osteoblastic bone lesions and mild demyelinating polyneuropathy in the lower limbs. Laboratory tests revealed the existence of thrombocytosis, polyglobulia, increased VEGF (1000 pg/mL) and IgA lambda M component (0.59 g/dl). An excisional biopsy of an axillary lymph node and bone marrow biopsy were performed. After diagnosis the patient was followed-up and showed a stable M component. Last clinical comment: Watch and wait.

Biopsy Fixation Details

Both the lymph node and bone marrow biopsies were fixed in formalin. Bone marrow core biopsy was EDTA decalcified. There is no available frozen tissue of any of the biopsies.

Frozen Tissue Available

NA

Details of Microscopic Findings

Lymph node biopsy disclosed grade 3 germinal center regression and plasmacytosis. Prominent dendritic cells were observed (grade 2) as well as slight hypervascularization (G1). IHC showed a sheet-like monotypic IgA lambda plasma cell population. HHV-8 was negative.

Bone marrow biopsy was slightly hypercellular with megakaryocytic hyperplasia and a nodular interstitial lymphoplasmacytic infiltrate. Immunohistochemistry showed expression of CD20, CD138 and lambda light chain restriction with IgA expression in the terminally differentiated cells. CCND1 and CD56 were negative. FCM of the bone marrow aspirate showed 0.57% plasma cells, of which 0.04% are lambda restricted, with decreased CD45 and negative CD19.

Immunophenotype

see above

Cytogenetics

46,XX[20].

Molecular Studies

Molecular analysis of JAK2, CALR and MYD88L265P were negative.

Ig clonality analysis in the lymph node using Euro clonality Biomed2 protocol showed clonal rearrangements of the IgH (FR2, 259 bp).

Proposed Diagnosis

Paraneoplastic Plasma cell type Castleman disease like histopathological features in plasma cell neoplasia/POEMS syndrome.

Interesting Feature(s)

- Multicentric lymph nodes with plasma cell type Castleman disease histopathological features in association with POEMS syndrome. High grade of Germinal center regression and absent germinal hyperplasia (PMID: 36690434).
- Sheets of monotypic IgA+ plasma cells in the lymph node with clonal Ig gene rearrangements. Monotypic lymphoplasmacytic cell population (IgA lambda) in the bone marrow biopsy.
- Follow-up. Stable M component without specific treatment. Watch and wait.
- Light and heavy chain IHC and Ig clonality analysis in lymph node biopsies with Castleman disease like features may identify plasma cell neoplasia/POEMS associated Castleman disease.

EA4HP24-LYWS-143

Multicentric Castleman's disease (MCD) with HHV8+/EBV+ plasmablastic proliferation.

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Case Description

May 2020: a 22-year-old HIV-negative African male presented with worsening fatigue and was diagnosed with autoimmune hemolytic anemia. Significant splenomegaly (23 cm) and multiple abdominal lymphadenopathy (up to 5 cm) were also observed. Infectious work-up revealed elevated HHV8 DNA (3256 UI/ml), low EBV DNA load with positive VCA IgM and IgG. A core biopsy of a retroperitoneal lymph node was performed, and a diagnosis HHV8-associated multicentric Castleman's disease was made (MCD). The patient was started on weekly Rituximab for 8 administrations combined with steroids, with progressive clinical improvement.

In March 2022, autoimmune hemolytic anemia recurred, along with an increase in lymphadenopathy. Therefore, steroid therapy and RCHOP treatment were initiated. An excisional biopsy of an axillary lymph node was performed, and the histological findings were consistent with MCD with HHV8^{+} EBV^{+} plasmablastic proliferation. Subsequently, the patient received 8 cycles of rituximab, initially showing a good response on PET scan, but later experiencing disease relapse. In September 2023, an additional core biopsy of a retroperitoneal lymph node was performed, showing histological features similar to the

previous biopsy. The patient was lost to follow-up for a few months but presented for a visit in December 2023 in overall good clinical condition.

Biopsy Fixation Details

Neutral buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

2020 retroperitoneal lymph node (core biopsy): involuted follicles, sheets of interfollicular plasma cells, and scattered plasmablasts located in the mantle cell zones. 2022 axillary lymph node (excisional biopsy - submitted material): the lymph node showed an overall preserved structure, containing numerous follicles, some with Castleman features. There were plasmablasts - scattered or in small aggregates - in the interfollicular zones and within the mantle zones, outside the germinal centers. The paracortex was expanded, predominantly populated by medium-sized T-lymphocytes. Vascular proliferation and plasma cell aggregates were also present in interfollicular areas. 2023 retroperitoneal lymph node (core biopsy): involuted follicles, scattered plasmablasts.

Immunophenotype

2020: HHV8$^+$ scattered plasmablasts. EBV (by in situ hybridization) was negative.
2022 & 2023: plasmablasts were HHV8$^+$ EBV$^+$, CD20-, PAX5+, IRF4+, CD38+, IgM+, with no evident expression of kappa and lambda light chains. The interfollicular plasma cells were polytypic as well. The interfollicular T-cell component was mainly composed by CD4+/PD1+ cells (CD3+, CD2+, CD7-/+).

Cytogenetics

Not done.

Molecular Studies

Polimerase chain reaction (BIOMED-2 protocol): polyclonal IGH, IGK and TRG rearrangement. Targeted next generation sequencing (146 lymphoma-associated genes): no mutations were detected.

Proposed Diagnosis

MCD with HHV8$^+$ EBV$^+$ plasmablastic proliferation.

Interesting Feature(s)

The present case poses a dignostic challenge regarding the distinction between MCD with plasmablastic aggregates (previously termed 'microlymphoma'), germinotropic LPD (GLPD), and extra-cavitary PEL. In MCD, the HHV8$^+$ plasmablasts may coalesce forming aggregates as the disease progresses, but they are usually EBV-. The distribution of the HHV8$^+$ EBV$^+$ cells of our case (mainly located outside the germinal centres) was not consistent with a GLPD. Interestingly, EBV was negative in the 2020 biopsy. The present case, along with other similar reports (Seliem *AJSP* 2007; Wang *Histopathology* 2017; Granai *Histopathology* 2021), suggests that the spectrum of HHV8$^+$ EBV$^+$ LPDs may be wider than expected.

EA4HP24-LYWS-146

86-year-old HIV+ man with KSHV+ multicentric Castleman disease and primary effusion lymphoma

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Case Description

An 86-year-old man with a history of HIV infection presented with recurrent unilateral pleural effusions (PE), diffuse lymphadenopathy (largest node measured 2.7cm) and splenomegaly. The patient was on treatment with Odefsey, his viral load was undetectable by NAAT. Absolute CD4 count was 212 cells/uL. The patient had no history of Kaposi sarcoma. The PE was evaluated by cytology multiple times in prior months and showed only mesothelial cells, lymphocytes and monocytes; no malignant cells were seen. An axillary lymph node biopsy was performed and showed KSHV/HHV8+ Multicentric Castleman disease (MCD; submitted case). The patient was treated with rituximab. He represented 2 years later with recurrent unilateral PEs and incidentally found to have metastatic colon cancer. The pleural fluid showed KSHV/HHV+ EBV neg primary effusion lymphoma (PEL).

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections show distortion of normal nodal architecture. The interfollicular area contains a significant number of plasma cells. Many follicles are involuted and hyalinized, and often associated with vessels which enter germinal centers perpendicularly. The vasculature is prominent, particularly in the interfollicular area. Associated with follicles and germinal centers are medium-sized, "plasmablastic" appearing cells. This specimen's histologic features are most consistent with MCD. The PEL consisted of monotonous large atypical lymphoid cells with a moderate amount of cytoplasm. Apopotic bodies are present.

Immunophenotype

Lymph node (LN): Immunostains show CD20+ B cells focally present in, and scattered outside, follicles. CD138+ plasma cells are numerous and primarily interfollicular. The plasma cells are polytypic. IHC for KSHV/HHV8 (LANA) shows numerous positive cells predominantly associated with follicles; a number of these cells are also vIL6 positive. EBER ISH for EBV was negative.

Pleural effusion (PE): Immunostains show neoplastic cells are negative for CD20, CD79a, CD10, BCL6, CD38, cytokeratin, are partial positive for CD45, CD138, and are positive for

MUM1. Some cells appear to be IgM+, but lack kappa and lambda light chains. The cells were LANA+ and EBER.

Cytogenetics

No

Molecular Studies

LN (A): PCR analysis pending.

PE (B): PCR gene rearrangement analysis showed polyclonal Ig heavy chain, monoclonal Ig kappa light chain, and clonal T cell receptor gamma chain in a polyclonal background. IGH mutation rate: 8.22% (>3% positive).

Proposed Diagnosis

LN (A): KSHV-MCD

PE (B): PEL, KSHV/HHV8+, EBV negative

Interesting Feature(s)

This case follows an HIV+ elderly man who developed KSHV-MCD, without KS, and subsequently developed PEL.

Although KSHV-MCD findings are classic for KSHV-MCD in an HIV patient, development of his PEL was unusual. Review of the literature (Barone, presentation EAPH-SH meeting 2022, Florence) shows PELs in the HIV setting are usually EBV+ (>75%), but in the non-HIV setting, where most patients are older, ~75% are EBV-. Thus, this patient's PEL shows features more consistent with PEL arising in a non-HIV setting. In addition, the expression of IgM raises possibility of a KSHV+ diffuse large B cell lymphoma, NOS, however, these cases are usually lambda positive and dim CD20+. A recent study (Lurain, et al, Blood 2019; 1753) showed EBV negative PELs have a poorer prognosis compared to EBV+ PELs. However, whether these cases exhibited unusual features is not clear. The patient underwent a hemicolectomy for his colon cancer but rapidly declined clinically. He entered palliative care and passed away 2 months after his PEL diagnosis.

EA4HP24-LYWS-147

Follicular Dendritic Cell sarcoma arising from Castleman disease, hyaline vascular variant, in a 60-year-old female

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Northwell Health/Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Pathology and Laboratory Medicine, Greenvale, USA

Case Description

A 60- year- old female with a history of recurrent endometrial cancer status post hysterectomy, presented with a lung mass suspicious of non-small cell carcinoma. PET/CT Chest demonstrated a FDG avid 4.7 x 3.6 x 5.2 cm (AP x TRV x CC) heterogeneous right paratracheal mass and a stable 1.1 cm triangular/nodule within the posterior left upper lobe.

The patient underwent an FNA of the paratracheal mass, followed by an excisional biopsy. The portion of tissue was also submitted for flow cytometric studies, molecular studies (for B-and T-cell gene rearrangement), and genomic profile testing.

Biopsy Fixation Details

The excisional biopsy was fixed in 10% neutral buffered formalin solution overnight.

Frozen Tissue Available

None

Details of Microscopic Findings

The histologic section is composed of lymphoid tissue showing diffuse proliferation of spindled to ovoid cells forming fascicles, storiform arrays and whorls.

The neoplastic cells are medium to large in size, with oval to elongated nuclei, with vesicular chromatin, small distinct nucleoli, delicate nuclear membrane, and moderate amount of eosinophilic cytoplasm. Many pleomorphic binucleated and multinucleated tumor cells are seen. Occasional mitotic figures are noted. There are no areas of necrosis seen and the tumor is infiltrated by small lymphocytes. There are adjoining areas showing follicles with regressed / atrophic germinal centers and some of the follicles show eosinophilic hyaline material deposition, reminiscent of Castleman like features.

Immunophenotype

Neoplastic cells are:

Positive: CD21 (strong), CD35 (diffuse), Fascin (subset), CXCL13, clusterin, MNDA, CD4 (partial), EMA (weak) and vimentin. The proliferation index (Ki-67) is approximately 5% in the neoplastic areas.

Others: CD163, and CD68 highlights many histicoytes. Residual follicles are positive for CD20, PAX5, CD79a, OCT2 and BOB1. BCL6 and CD10 highlights residual germinal center. The proliferation index (Ki-67) is high in the residual follicles.

Cytogenetics

46 XX; Normal Female karyotype

Molecular Studies

B- cell gene rearrangement:

IgH gene Status: NEGATIVE

IgK gene Status: NEGATIVE

T-cell gene rearrangement:

TCR-gamma: NEGATIVE

FoundationOne heme genomic findings:

TNFAIP3 K759fs*57

Tumor Mutational Burden - 1 Muts/Mb

Proposed Diagnosis

Follicular Dendritic Cell sarcoma arising from a background of Castleman's disease, hyaline vascular variant.

Interesting Feature(s)

Follicular dendritic cell sarcoma (FDCS) are rare, low- to intermediate-grade malignant neoplasm, composed of neoplastic proliferation of spindled to ovoid cells with morphologic and immunophenotypic features similar to normal follicular dendritic cells. Approximately 10% to 20% of FDCS cases are associated with antecedent or

concurrent Castleman disease, mostly the hyaline vascular variant, as seen in our case. FDCS, sometime the accurate diagnosis could be very challenging and this entity is often initially misdiagnosed, especially when examined in small biopsy specimens. We herein report a rare case of FDCS arising in the paratracheal region that was initially misdiagnosed as carcinoma on an FNA specimen.FDCS exhibits distinctive histologic features that permit its presumptive recognition, but a firm diagnosis requires confirmation with immunohistochemistry and genomic studies are helpful. Genomic studies detected TNFAIP3 K759fs*57, which has been previously reported and supports the association of FDSC and NF-KB pathways.

EA4HP24-LYWS-155

Follicular dendritic cell (FDC) sarcoma arising from hyaline vascular-unicentric Castleman disease (HV-UCD) with TdT+ cells present.

Dr. Andrew G. Evans

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Case Description

A 42-year-old female had a pelvic mass palpated during routine annual gynecologic exam. She was status-post trans-vaginal hysterectomy (ovarian-sparing) 5 years prior for severe menorrhagia. Ultrasound revealed a 5 cm lobulated mass. CT scan showed similar findings, while confirming a retroperitoneal location. Core needle biopsy was non-diagnostic. On exploratory laparotomy, the surgeon felt the mass represented an enlarged lymph node and complete excision was performed.

Biopsy Fixation Details

Tissue was preserved in 10% buffered formalin. Fresh tissue was also submitted for flow cytometry.

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections show a prominent spindled cell tumor mass arising from lymph node parenchyma. The main tumor mass is composed of sheets of spindled to polygonal cells with pale eosinophilic cytoplasm, irregular vesicular nuclei, and many with ill-defined cells borders, conferring a syncytial appearance. There is a sparse lymphoid infiltrate throughout much of the spindled cell tumor, which is focally separated from lymph node parenchyma by a fibrotic capsule, but elsewhere these spindled cells blend subtly into the lymph node cortex. The remaining lymph node architecture throughout is abnormal, exhibiting atretic germinal centers with plump enlarged follicular dendritic cells (FDCs). Many of these structures contain penetrating sclerotic blood vessels (“lollipop sign”) and prominent rings

of small lymphocytes ("onion-skinning"), with occasional twinning of abnormal germinal centers.

Immunophenotype

Neoplastic spindle cells were positive by IHC for CD21, CD35, and focal EMA, while negative for CD3, CD20, desmin, SMA, D240, inhibin, AE1/AE3, calretinin. Background lymph node elements with atretic germinal centers were negative for HHV8 (LANA) but contained scattered TdT-positive cells. By flow cytometry, no monotypic B-cell or aberrant T-cell population was identified.

Cytogenetics

None available.

Molecular Studies

None available.

Proposed Diagnosis

Follicular dendritic cell (FDC) sarcoma arising from hyaline vascular-unicentric Castleman disease (HV-UCD), HHV8-negative, with TdT+ cells present.

Interesting Feature(s)

Rare presentation of FDC sarcoma arising from a dysplastic proliferation of FDC cells in HV-UCD. This finding highlights the relationship between altered (even neoplastic) FDC biology in the etiology of HV-UCD. At the same time, the presence of TdT+ lymphoid cells is a rarely-reported enigmatic event known to occur in HV-UCD, and is also seen in this case.

EA4HP24-LYWS-157

HHV-8-positive, HIV-negative, multicentric Castleman disease with simultaneous lymph node Kaposi sarcoma.

Francisca Emanuel Costa

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Case Description

Male patient, 75 years of age.

Past medical history: hypertension, type II *Diabetes mellitus*, aortic stenosis, lacunar stroke in 2010, colon diverticulosis, right nephrectomy in 2019 for renal atrophy and prostate adenocarcinoma Gleason score 6 (3+3) diagnosed in 2019 and submitted to brachytherapy. Usual medication: Clopidogrel, 75mg; Rosuvastatin, 10mg; Indapamide + Amlodipine, 1.5mg+5mg; Trimetazidine, 35mg; Empagliflozin, 10mg and Metformin, 700mg.

History of present illness (February/2023): on imaging exams (Angio-CT), there are multiple lymphadenopathies accidentally detected and further characterized on CT-scan: a left supraclavicular lymph node measuring 2.5cm in long axis, multiple left axillary lymphadenopathies, in the superior mediastinum and retroperitoneal lymphadenopathies.

No other symptoms. Serum C-reactive protein 10mg/L, IgA 520mg/dL and IgM 402mg/dL. HIV-negative.In May/2023, the patient underwent excisional biopsy of the axillary lymph nodes.

Biopsy Fixation Details

We received a fresh specimen consisting of adipose tissue weighing 8g, from which two lymph nodes measuring 1.5cm and 2.5cm in long axis were dissected. Both lymph nodes had central adipose transformation and fleshy, pinkish parenchyma and were left to fix in 10% buffered-formalin overnight.

A small section of fresh lymph node tissue was sent to flow cytometry laboratory.

Frozen Tissue Available

None available.

Details of Microscopic Findings

On microscopic evaluation, there is fatty transformation of the lymph nodes and the lymphoid parenchyma shows partially preserved architecture with the presence of lymphoid follicles in varying degrees of involution, some with atretic germinal centers and the frequent presence of venules penetrating the germinal centers (lollipop follicles). The follicles have prominent mantle zones with lymphocytes frequently organized in concentrical layers (onion skin appearance) and that occasionally intrude into the germinal centers and efface them. There is an expansion of the interfollicular region with marked vascular proliferation of high endothelial venules with perivascular hyalinization and plasmacytosis. There are rare large cells around the mantle regions, without evidence of sheets of plasmablasts or plasma cells besides the mantle zones.Additionally, one of the lymph nodes has a 2.5mm mesenchymal neoplasia with intervening vascular spaces filled with blood. The spindle cell cells have mild to moderate pleomorphism and there are occasional intracytoplasmic hyaline globules. There is only one recognizable mitotic figure, but no necrosis. Hemosiderin pigment is also identified.

Immunophenotype

The immunohistochemical study highlights the presence of HHV-8-positive cells in the mantle zone, in the interfollicular region and in endothelial cells of high endothelial venules and reveals the polytypical nature of the plasma cells (Kappa/Lambda, CISH).

There is no immunohistochemical evidence (CD20, PAX5, CD79a, CD3, CD5, CD21, CD23, CD10, Bcl-6, Bcl-2, Cyclin D1, Ki-67) of lymphoma.

The 2.5mm nodule presents CD31, CD34, ERG and podoplanin immunoreactivity and nuclear staining for HHV-8.Flow cytometry detected no changes in the immunophenotype of lymphocytes that were suggestive of lymphoma.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

HHV-8-positive, HIV-negative, multicentric Castleman disease with simultaneous lymph node Kaposi sarcoma.

Interesting Feature(s)

Previously asymptomatic patient.

Concomitant diagnosis of HHV-8-positive multicentric Castleman disease and Kaposi sarcoma in a lymph node of a HIV-negative patient.

EA4HP24-LYWS-159

HHV8 negative Castleman disease, mixed hyaline vascular variant and plasma cell variant, stroma-rich, with progression to B-cell lymphoma

Dr. Shaoying Li, Dr. Jie Xu, Dr. Pei Lin, Dr. Roberto Miranda, Dr. L. Jeffrey Medeiros

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Case Description

•A 35-year-old woman with 1.5 years of B symptoms and enlarged retroperitoneal lymph nodes. Previous biopsies were non-diagnostic with an atypical lymphoplasmacytic proliferation with sclerotic changes. The patient received rituximab x 4 and prednisone

•CBC: WBC 10.3 K/ul, Hgb 7.5 g/dL, MCV 78 fL, Platelet: 696 K/ul

•Elevated total serum protein, no M-spike on SPEP/IFE, elevated serum IgG (4297mg/dL) and IL-6

•A retroperitoneal excisional biopsy was performed.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Nodal architecture effaced by a diffuse lymphoplasmacytic infiltrate with vascular and stromal proliferation, including stroma-rich, plasma cell-rich and both rich regions. There were few remnants of germinal centers as highlighted by CD23 stain.

Immunophenotype

Immunohistochemistry showed: CD3+ small T cells and CD20+ small B cells admixed with polytypic plasma cells. Rare plasma cells were positive for IgG4. EBER and HHV8 were negative. Remnants of residual follicles were highlighted by CD20, CD21 or CD23 and BCL6. TdT was expressed in CD3 strongly positive blastoid small lymphocytic clusters. Flow cytometry immunophenotypic analysis showed no aberrant B or T cells.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Diagnosed as: HHV8 negative Castleman Disease, with mixed features of hyaline vascular variant and focal plasma cell variant, stroma-rich

Symptoms resolved after the excisional biopsy. On observation and lost follow up after 1 year. Symptoms recurred 5 years later. Staging PET showed FDG-avid retroperitoneal lymph node. Serum IL-6 level was elevated. A retroperitoneal lymph node excisional biopsy was performed. Histologic sections showed enlarged lymph node with a vague nodular to focally diffuse lymphoid proliferation. The lymphoid cells are variable in size with irregular nuclear membrane and relatively pale cytoplasm. Focally, scattered reactive follicles and clusters/sheets of plasma cells were present. Immunohistochemistry showed most cells were CD20+/PAX5+ B cells with aberrant CD43 expression and no CD21 positive follicular dendritic cell meshwork. Ki67 showed a proliferation rate of ~30%. A few residual reactive follicles were highlighted by CD20, CD21, BCL2 and BCL6 stains. Plasma cells were polytypic by kappa and lambda ISH. EBER and HHV8 were negative. Flow cytometry studies showed: an aberrant B cell population positive for CD11c, CD19, CD20bri, CD22, CD38, CD43, CD44, CD20, negative for CD5, CD10, CD23, CD30, and surface light chains Diagnosed as: CD5-, CD10- B-CELL LYMPHOMA in a background of focal HHV8 negative Castleman disease.

Final proposed diagnosis: HHV8 negative Castleman disease, mixed hyaline vascular variant and plasma cell variant, stroma-rich, with progression to B-cell lymphoma

Interesting Feature(s)

•Unicentric Castleman disease (UCD), HHV8 negative, with large area of hyaline vascular variant and focal plasma cell variant, stroma-rich

•Clinicopathologic features overlapped with reactive lymphadenopathy which caused difficulty in diagnosis.

•The UCD contained foci of TdT+ T-lymphoblastic proliferation. Knowing that indolent T-lymphoblastic proliferations can be seen in Castleman Disease will help to avoid a misdiagnosis of T-lymphoblastic lymphoma.

•UCD usually can be eliminated with surgical resection and usually has a good prognosis. Despite of that, this patient progressed to B cell lymphoma 5 years later.

EA4HP24-LYWS-163

TAFRO variant of idiopathic multicentric Castleman disease

Dr. Haipeng Shao, **Dr. Ling Zhang**

Moffitt Cancer Center, Pathology, Tampa, USA

Case Description

The patient is a 47-year-old previously healthy male presented with worsening shortness of breath, anasarca, and abdominal bloating. CT scan of chest, abdomen and peliv showed moderate-large left pleural effusion, small right pleural effusion, anterior mediastinal mass and numerous nonspecific subcentimeter shotty lymph nodes in the retroperitoneum and along the bilateral iliac vessels. The patient subsequently developed subdural hematoma,

and seizure status post right decompressive craniectomy, renal failure requiring hemodialysis. A bone marrow biopsy showed hypercellular marrow for his age with erythroid and megakaryocytic hyperplasia, and increased marrow reticulin fibrosis (MF2/3). Flow cytometry of the marrow was negative for clonal B-cell or plasma cell population, and negative for blastosis. Cytogenetic study showed a normal male karyotype, 46,XY[20]. NGS with Integrated Oncology IntelliGEN Myeloid panel was negative. The patient was treated with Siltuximab as first-line therapy for iMCD. Follow-up CT scan showed improvement in lymphadenopathy 1 year post therapy.

Biopsy Fixation Details

10% formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

The lymph node showed marked nodal architecture distortion with prominent high endothelial vascular proliferation and large clusters and sheets of mature plasma cells between the vasculatures. Multiple well separated reactive regressed lymphoid follicles are present. There are scattered immunoblasts in the interfollicular areas.

Immunophenotype

CD20 and PAX5 highlighted multiple lymphoid folliclesCD10 highlights diminished germinal centers. CD3 showed interfollicular T cell with predominance of CD4 positive T cells and fewer CD8 positive T cells. There was a subset of follicular T helper cells that were positive for ICOS and weakly PD1. CD21 highlighted tight follicular dendritic meshworks of the follicles, without significant extrafollicular expansion. CD138 highlighted large numbers of plasma cells. The plasma cells were polyclonal for kappa and lambda light chains by in situ hybridization studies. The plasma cells were positive for IgG, with only rare IgG4 positive plasma cells. HHV8 was negative. The EBER was negative for EBV infection.

Cytogenetics

N/A

Molecular Studies

PCR studies performed on tissue sections showed no clonal B-cell or TCR beta or gamma gene rearrangements.

Proposed Diagnosis

TAFRO variant of idiopathic multicentric Castleman disease.

Interesting Feature(s)

The histology of the lymph node shows features of plasma cell variant of Castleman disease, including regressed germinal centers, sheets of interfollicular plasma cells and vascular proliferation. The prominent proliferation of high endothelial venules is typically seen in TAFRO variant of iMCD. The diagnosis of TAFRO syndrome requires the presence of at least 3 of the 5 FAFRO symptoms: thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis and renal insufficiency (R), and organomegaly/lymphadenopathy (O), in addition to the morphologic findings of the lymph node consistent with idiopathic Castleman disease. The megakaryocytic hyperplasia in the bone marrow is also considered a minor criterion. [ZL1] The main differential diagnosis is angioimmunoblastic T-cell lymphoma, which shows

similar clinical presentation but was ruled out based on the absence of clonal T-cell gene rearrangements.
REF: Semra Paydas. Tafro syndrome: Critical review for clinicians and pathologists. Crit Rev Oncol Hematol. 2018 Aug:128:88-95.
[ZL1]Reference?? Not sure it is included, see attached review paper

EA4HP24-LYWS-169

EBV-associated reactive hyperplasia with Castleman-like features and subsequent progression to classic Hodgkin lymphoma

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Case Description
A 54-year-old female with history of smoking, type II diabetes and recent dental and upper respiratory tract infections presents with an enlarged neck node and intermittent fatigue. She denies other systemic symptoms. She has no history of immune deficiency. Imaging shows a right neck node measures up to 2.9 cm in size with multiple additional enlarged, FDG avid right neck nodes (SUVs up to 17.4).
Biopsy Fixation Details
Formalin fixed, paraffin embedded
Frozen Tissue Available
None
Details of Microscopic Findings
Enlarged lymph node with scattered, largely atretic germinal centers with occasional twinning. Vague onion skinning of the mantle zones can be appreciated. The paracortex is expanded by lymphocytes, numerous plasma cells, histiocytes and vascular elements, some of which are sclerotic. The lymphocytes are predominantly small to medium in size with focal expansion of monocytoid B-cells. Scattered immunoblasts with prominent nucleoli, which are predominantly mononuclear. Increased capsular fibrosis with occasional sclerotic bands.
Immunophenotype
CD3, CD5, CD20 and CD79a show overall retained lymphoid architecture. CD21 and Bcl6 highlights regressed follicles with increased dendritic cells. CD30 shows increased immunoblasts with dim Pax5 and negative for CD15. CISH for EBER shows positivity in focal follicles and scattered staining in the paracortex in lymphoid cells ranging in size. An ultrasensitive kappa/lambda dual CISH stain shows polytypic plasma cells and B-cells. IgG4+ plasma cells are focally increased. HHV8 LANA1 and ALK are negative. CD4 and CD8 show a mixed population. ICOS+ T-cells are focally expanded without an increase in

PD-1. TdT shows scattered positivity. CD123 shows slightly increased plasmacytoid dendritic cells. Flow cytometry: no evidence of a monoclonal B-cell or aberrant T-cell population; CD4:CD8 ratio 3.4.

Cytogenetics

Not performed

Molecular Studies

Negative for T-cell clonality by PCR

Subsequent lymph node involved by classic Hodgkin lymphoma evaluated by NGS (GenPath Onkosight): MAP2K1 variant of unknown significance ,VAF 46%. No clinically relevant TierI/II variants were identified

Proposed Diagnosis

EBV-associated reactive hyperplasia

Interesting Feature(s)

EBV+ reactive hyperplasia in an otherwise healthy immune competent patient is unusual but described (Dojcinov et al. Blood. 2011;117:4726). In addition, the patient's history of active smoking may affect immune function and increase risk of EBV reactivation (Open Forum Infect Dis. 2022;9(5):ofac128). The prominent Castleman-like features (regressed germinal centers, twinning, onion-skinning, plasmacytic hyperplasia) is a rare pattern previously described for EBV-associated reactive hyperplasia (6% of cases, Dojcinov et al.). Monocytoid B-cell reaction is common. Both EBV patterns (restricted to follicles and paracortical) are seen in this case. The increased IgG4 positivity is also intriguing. Another interesting feature of this case is its evolution to EBV+ classic Hodgkin lymphoma, nodular sclerosis subtype. Approximately 6 months after this biopsy, the patient developed cough and B-symptoms with low grade fever and intermittent night sweats. Repeat PET/CT showed interval enlargement and FDG avidity of right cervical lymph nodes. She received chemotherapy with four cycles of AAVD regimen (Brentuximab vedotin, Doxorubicin, Vinblastine, and Dacarbazine) with post treatment PET/CT showing complete remission. The patient is now disease free >18 months. Evolution to CHL was also seen in 2/31 cases described by Dojcinov et al., but they were of mixed cellularity subtype.

EA4HP24-LYWS-171

Kaposi sarcoma and concomitant KSHV-associated multicentric Castleman disease (KSHV-MCD) in the setting of HIV infection.

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Case Description

An HIV+ 36-year-old male with poor compliance to HAART therapy presented with widespread painful skin and mucosal lesions, and persistent fevers. His labs were significant for WBC count 2.8 K/uL, Hb 7.4 g/dL, platelets 132 K/uL, CD4 count 27cells/uL (normal range 500-1400 cells/uL), interleukein-6 33.6pg/ml (normal <7pg/ml), HIV viral load of 54 copies/ml, EBV titers of 2200 IU/ml and HHV-8 quantitative PCR assay of 192,000 copies/ml along with elevated LDH (673 U/L) and CRP levels (50mg/L). Imaging demonstrated generalized lymphadenopathy and hepatosplenomegaly. A cervical lymph node biopsy revealed concomitant KSHV/HHV8+ multicentric Castleman disease or KSHV MCD and KS.

Biopsy Fixation Details

Excisional biopsy of cervical lymph node fixed in formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections of the lymph node showed foci of spindle cell proliferation, with poorly formed, slit-like vascular channels and extravasated red blood cells.

The background lymph node shows variably-sized, reactive-appearing secondary follicles and some atretic follicles. The attenuated mantle zones contain individually scattered, large, transformed cells. The interfollicular areas show increased vascularity, paucity of lymphocytes and variable plasmacytosis.

Immunophenotype

Immunostains for HHV8 (LANA) and CD34 highlight the spindle cell proliferation and vascular channels within the lymph node and surrounding fibroadipose tissue, confirming presence of Kaposi sarcoma.

HHV8 also highlights scattered immunoblasts and plasmablasts within the mantle zones as well as in the interfollicular areas. These large cells are negative for EBER (by ISH staining).These cells are MUM1+, CD138-, and appear to preferentially express IgM and lambda (by ISH staining). The interfollicular plasmacytosis is predominantly IgG+ and is polytypic for kappa and lambda.

Cytogenetics

Karyotype failure

Molecular Studies

None

Proposed Diagnosis

Kaposi sarcoma and concomitant KSHV multicentric Castleman disease in the setting of HIV infection.

Interesting Feature(s)

KS is the most common neoplasm encountered in HIV infected patients. An association between HIV infection and MCD has been noted since the onset of the AIDS epidemic. There is a significant association between KS development, HHV-8 KSHV and HIV infections. About 50%-70% of HIV-infected patients who are coinfected with HHV-8 develop KSHV-MCD[1].

This case shows characteristic clinical and immunomorphological features of KSHV-MCD and KS presenting in the setting of HIV infection. In addition to the widespread, multifocal lesions involving the hard palate and extremities, the patient presented with persistent fevers, hepatosplenomegaly, and constitutional symptoms. Laboratory data showed high HHV-8 viral load, elevated IL-6, CRP, anemia, and thrombocytopenia. Morphologically, a mixture of hyperplastic and involuted follicles is seen, with interfollicular vascular proliferation and polytypic plasmacytosis. KSHV-infected, large mononuclear cells are seen within the mantle zones. These cells demonstrate monotypic expression of IgM and lambda as typically seen in KSHV MCD.

EA4HP24-LYWS-181

BCL2-R-negative CD23-positive follicle center lymphoma with Hyaline-Vascular Castleman Disease-like features

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Case Description

A middle-aged lady presented with right inguinal lymphadenopathy. No systemic or constitutional symptom was reported. She had history of low-grade appendiceal mucinous neoplasm and underwent right hemicolectomy. She also had history of psoriatic arthropathy and had previously been prescribed multiple disease-modifying antirheumatic drugs (DMARD) and biologics. Whole-body FDG PET-CT showed generalized lymphadenopathy, with multiple hypermetabolic lymph nodes found at lower para-aortic, paracaval, bilateral common iliac, right external iliac, right inguinal, right parasternal, mediastinal, hilar, left axillary and left upper neck areas, radiologically suspicious for recurrent tumors. Excisional biopsy of the right inguinal lymph node was performed.

Biopsy Fixation Details

Overnight fixation by buffered formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections showed a lymph node partially effaced by follicular and diffuse-patterned lymphoid proliferation. High endothelial venules were significantly increased in the interfollicular areas. The follicles were variably sized, mostly showing small regressed germinal centers that were surrounded by expanded mantle zones. Twinning of germinal centers and hyalinized vessels radially traversing into germinal centers were seen. The germinal centers and interfollicular areas showed mainly small-sized centrocytes with angulated nuclear contours and scant cytoplasm. Occasional large-sized centroblasts were seen. Areas of diffuse pattern were present.

Immunophenotype

Immunostains showed a diffuse proliferation of CD20+, small-sized B cells encompassing the follicles and interfollicular areas, admixed with some CD3+ T cells. The population of B cells was also diffusely positive for CD10, BCL6 and CD23. They are negative for BCL2. While immunostain for CD21 highlighted presence of follicular dendritic cell meshwork in some atretic follicles, a significant proportion of follicles showed absence of follicular dendritic cell meshwork. The areas of diffuse pattern also lacked follicular dendritic cell meshwork.

Cytogenetics

N/A

Molecular Studies

Clonal immunoglobulin light chain gene rearrangement was detected on PCR. FISH for BCL6 and BCL2 gene rearrangements was negative.

Proposed Diagnosis

Follicular lymphoma, predominantly diffuse growth pattern (WHO 5th ed.) / BCL2-R-negative CD23^{+} follicle center lymphoma (ICC) with Hyaline-Vascular Castleman Disease-like features

Interesting Feature(s)

This case highlighted a morphological variant of follicular lymphoma prone to misdiagnosis, which can greatly affect subsequent management of these patients. While cases of follicular lymphoma with Hyaline-vascular Castleman Disease-like morphology have been documented in literature, most of those cases (if not all) demonstrated presence of BCL2 gene rearrangement. Moreover, follicular lymphoma with predominantly diffuse pattern usually presented with limited stage disease, yet this case showed an atypical clinical presentation of generalized lymphadenopathy. Numerous theories have been proposed regarding the occurrence of Hyaline-Vascular Castleman Disease-like features, including lymphoma cells involving previously reactive lymph nodes, or lymphoma cells inducing Hyaline-Vascular Castleman Disease-like changes.

EA4HP24-LYWS-185

Monoclonal Plasma Cell Proliferation in a Case of Castleman Disease

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Case Description

73-year-old woman with a past medical history of unicentric Castleman's Disease (UCD) as follows:

2008 excision: Florid hyperplasia of the lymph node with features suggestive of Castleman Disease (mixed hyaline and plasma cell proliferation), with flow cytometry showing polytypic plasma cells.

2015 incisional biopsy: Castleman disease (CD), hyaline vascular (HV) type, with flow cytometry showing polyclonal B cells and T cells with no antigen loss.

She was treated with multiple therapies including siltuximab, rituximab, and eventually chemotherapy with initial responses. However, in 2018, she had recurrent right cervical lymphadenopathy with no night sweats, fever, chills, pain, or additional lymphadenopathy, and underwent a right neck dissection in 2019.

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

NA

Details of Microscopic Findings

A right neck dissection (2019) revealed an enlarged lymph node with numerous lymphoid follicles containing mantle zones with "onion skin" appearance and atretic germinal centers. A few radially penetrating vessels within lymphoid follicles ("lollipop follicles"), occasional interfollicular hyalinized vessels, and interfollicular sheets of plasma cells with no overt morphologic atypia are also seen.

Immunophenotype

CD20+ Pax5+ small B-cells are located mainly within lymphoid follicles associated with intact CD21+ FDC meshworks. B-cells in the germinal centers are BCL6+ BCL2-. CD3+ CD5+ small T-cells are mainly seen in the interfollicular areas. The interfollicular areas contain focal sheets of CD138+ MUM1+ IgA+ lambda+ kappa- plasma cells; only a few IgM+, IgG+, and/or IgG4+(<50/hpf) plasma cells are identified. HHV-8 IHC and EBER ISH are both negative. Flow cytometry was not performed.

Cytogenetics

FISH panel of plasma cell myeloma probes: Negative

Molecular Studies

IGH gene rearrangement studies by PCR: Positive for monoclonal rearrangements in frameworks 2 and 3.

Gene sequencing studies (40 gene panel): Negative for disease associated variants and variants of uncertain significance.

Proposed Diagnosis

Castleman disease with mixed histopathologic features of the hyaline vascular and plasma cell types, and monoclonal plasma cells. Close follow-up and further work-up to evaluate the possibility of a plasma cell neoplasm was recommended. However, the patient was lost to follow up.

Interesting Feature(s)

Most cases of UCD are of the HV type (80-90%), while the plasma cell (PC) and mixed types are seen less frequently. Admixed plasma cells are generally polyclonal in HV type. Monoclonal plasmablasts in the mantle zone are commonly seen in the PC type of CD. However, a few PC type cases of CD (not associated with POEMS syndrome) with monoclonal IGH rearrangements and extensive light chain restriction (often lambda-restricted and IgG+ or IgA+) on plasma cells have been reported. Our case displayed sheets of IgA+ plasma cells with light chain restriction and monoclonal IGH gene rearrangements. Patients with UCD often benefit from resection of the involved site with high cure rates. However, our patient had multiple localized recurrences without additional sites of involvement, which raises the possibility of a different clinical behavior perhaps due to its association with clonal plasma cells. Case reports of CD associated with plasmacytomas are noted in the literature. Although our patient did not have any evidence of additional masses or lesions apart from that in the neck, she was lost to follow up, so the possibility of concurrent involvement by a plasma cell neoplasm or a B-cell lymphoma with extensive plasmacytic differentiation could not be completely excluded.

EA4HP24-LYWS-197

KSHV+ large B-cell lymphoma with EBV co-infection arising from multicentric Castleman disease (MCD) with concurrent Kaposi sarcoma (KS)

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Case Description

A 53 y/o man with a 25-year h/o HIV infection on HAART (VL 1,970 cpy/ml, CD4 374 cells/ul) was diagnosed at OSH with KS and KSHV-associated MCD over the past year before presenting to our hospital with fever and found to have sepsis, diffuse LAD, hepatosplenomegaly, and marked KSHV (>1.00E+08 cpy/ml) and EBV (1.2E+06 IU/ml) viremia. LN bx showed involvement by KS and KSHV+ EBV+ plasmablastic cells with a multifocal macronodular growth pattern and MCD in the background. Circulating

cytoplasmic λ+ plasmablastic cells (22% of WBCs) were detected by peripheral blood (PB) flow cytometric analysis and smears. The patient received 1 cycle R-EPOCH but deteriorated rapidly and passed away 1 mo after the lymphoma diagnosis.

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

LN: Nodal architecture is markedly distorted by a prominent atypical spindle cell proliferation, marked plasmacytosis, and multifocal macronodular to sheet-like aggregates of large atypical lymphoid cells that have plasmablastic cytomorphology. Many mature-appearing plasma cells and small lymphocytes are present in the background.

PB smears reveal large atypical cells with immunoblastic/plasmablastic cytomorphology.

Immunophenotype

LN: Neoplastic cells areCD20 weakly+/-, CD79a-, PAX5-, MUM1+, CD138-, IgM+, KSHV (LANA)+, EBER+, CD30+/-, CMYC+ (50%), P53+ (30%), CD10-, CD5-, Cyclin D1-, IgA-, IgD-, IgG-, λ (ish)+/-, and with elevated Ki-67. PAX5+/CD20+ small B-cells are decreased and seen in small atretic follicles. BCL6 & CD10 shows no definite GC. CD138, κ and λ-ISH highlight numerous background polytypic plasma cells. The atypical spindle cells are CD34+ and KSHV+.

PB: CD38+, IgM+, λ+ cells by flow.

Cytogenetics

Normal Karyotype. FISH analyses are negative for BCL2, BCL6, MYC, and TP53 rearrangement.

Molecular Studies

Identical clonal IgH gene rearrangements detected in LN and PB by PCR.

Proposed Diagnosis

1) KSHV+ large B-cell lymphoma with a multifocal macronodular growth pattern arising from MDC in association with HIV infection. (2) KSHV+ KS.

Interesting Feature(s)

We report a case with three concurrent KSHV-related pathologies, including large B-cell lymphoma (LBCL), MCD, and KS. KSHV+ DCBCL is a rare type of lymphoma and usually arises in association with immunodeficiency and KSHV+ MCD. Our patient has a long h/o HIV infection and a recent diagnosis of KSHV+ KS. The marked polytypic plasmacytosis and atretic B-cell follicles in the background of the current LN are c/w the prior diagnosis of MCD.

Our case shows a co-infection of KSHV and EBV in the large cells, which is uncommon for KSHV+ DLBCL but has been reported in a few cases (PMID: 17721201 & 12748248). Furthermore, the EBV positivity does not exclude a diagnosis KSHV+ DLBCL per WHO 5th edition. Considering B-cell lymphomas with frequent KSHV and EBV co-infection, we found extracavitary primary effusion lymphoma very unlikely because of the IgM and λ expression in lymphoma cells, growth pattern and the MCD background. We also considered germinotropic lymphoproliferative disorder (GLPD) and a lesion previously described as

KSHV+ microlymphoma (PMID: 17721201). However, given that our case shows clonal IgH, markedly disrupted nodal architectures with plasmablastic cells outside of follicles, and an aggressive clinical course with multiple enlarged LNs and leukemic component, our case likely represents a lesion closer to KSHV+ DLBCL than KSHV+ microlymphoma or GLPD in the spectrum of KSHV+ lymphoid proliferation. Our case highlights the complexity of KSHV-related pathologies and adds to the rare reports of KSHV+ LBCL with EBV co-infection.

EA4HP24-LYWS-199

Hyaline-vascular Castleman disease with exuberant stromal/vascular proliferation

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Case Description

The patient is a woman in her 50s with a history spanning over 30 years. In her late 20s-early 30s a mass was found in the right lower quadrant involving the mesentery and she underwent an exploratory laparotomy with incomplete tumor resection with a diagnosis of Castleman's disease. The patient is HIV negative and did not exhibit symptoms of TAFRO or POEMS. This mass recurred at the same site in 2015, 2018, and 2019. MRI revealed a 5.4 cm. A PET scan showed a larger right lower quadrant mass with an SUV of 7 without additional areas of FDG avidity.

The 2019 mass resection, reviewed at our institution, showed hyaline vascular Castleman disease with an exuberant stromal/vascular proliferation. Review of the patient's laboratory studies showed normalization of the patient's VEGF level, postoperatively.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Microscopic examination shows a well-defined but unencapsulated mass consisting of effaced follicles separated by bands of dense fibrotic, sclerosed, and hyalinized tissue. The follicles showed atretic germinal centers, and expanded mantle zones with concentrically arranged lymphocytes, imparting an onion skin appearance. There are varying degrees of hyalinization noted. No atypical large lymphocytic infiltrates are identified. In areas, there are prominent increased vascular proliferations in interfollicular areas with increased spindle cells. A prominent stromal proliferation is noted with a haphazard organization and with ovoid nuclei and vesicular chromatin. There are focal areas with an increased dendritic

cell in small clusters. Plasma cells are also noted but they are relatively infrequent, without confluent sheets.

Immunophenotype

CD20/ CD79a/PAX5: Positive in numerous B-cells highlighting follicles and expanded mantle zones
CD3/CD8: Positive in fewer numbers of T-cells
CD4: Positive in a large subset of T-cells
CD10: highlights regressed germinal centers
BCL2: Highlights expanded mantle zones, normal expression in T cells
CD21: Highlights focal areas of dendritic cell proliferation
CD23: Positive in mantle zone B-cells
CD43: Positive in T-cells, absent on B cells
HHV8: Negative
ALK1: Negative
CD138/MUM1: Positive in plasma cells
IgG: Positive in the majority of plasma cells
IgG4: Positive in rare cells, <40% of IgG+ plasma cells
Kappa (ISH)/Lambda (ISH): Polytypic expression
CD34: Highlights small vascular structures
D2-40: Highlights lymphatic space
S100: Highlights subset of dendritic cells
SMA: Highlights smooth muscle surrounding blood vessels
Ki-67/MIB1: Overall low proliferation index
EBER (ISH): Negative

Cytogenetics

Normal female karyotype.

Molecular Studies

Not performed

Proposed Diagnosis

Hyaline-vascular Castleman disease with exuberant stromal/ vascular proliferation.

Interesting Feature(s)

This is a relatively rare presentation of recurrent unicentric Castleman Disease, with an exuberant SMA+ stromal proliferation (stromal rich variant) of angiomyoid cells. No concurrent follicular dendritic cell tumor was present in this case. Unlike other subtypes, the stromal rich variant tends to occur in the adult population and involve the abdomen, rather than the peripheral lymph nodes or mediastinum.

EA4HP24-LYWS-205

Follicular dendritic cell sarcoma associated with hyaline-vascular Castleman disease – A case report

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Case Description

Fifty-seven years old female with a mesentery mass.

MRI: Posterior anterior vena cava occupation of the descending duodenum.

Biopsy Fixation Details

A well encapsulated mass measured 10 cm in greatest diameter was found behind the right side of the hepatoduodenal ligament.

The mass showed greyish cut surface, with medium texture, rich of small follicles/ nodules.

Frozen Tissue Available

NA

Details of Microscopic Findings

Area A: Germinal centers are lymphocyte-depleted and enriched in FDCs that may occasionally show dysplasia. Radially oriented hyalinized or sclerotic blood vessels penetrate into germinal centers forming hyaline-vascular lesions. Mantle zones are expanded with lymphocytes arranged in concentric rings around germinal centers.

Area B: Atypical FDCs hyperplasia.

Area C: The neoplastic cells show spindled, ovoid or epithelioid cell morphology, and are arranged in whorls, fascicles, syncytial sheets, nodules and storiform pattern. Tumour cells have moderate amounts of eosinophilic cytoplasm with indistinct cell borders creating a syncytial appearance. Nuclei are elongated with vesicular chromatin, delicate nuclear membrane and small but distinct nucleoli. The nuclei tend to be unevenly spaced and clustered. Some cells show prominent cytologic atypia with multinucleation and pleomorphic nuclei.

Immunophenotype

The atypical spindle cells: CD20-, CD3-, CD23+, CD35+, SMA-, desmin-, S-100-, DOG-1-, CD117-, CD34-, HHV-8-, Ki-67+ (30%)

ISH detection for EBER: Negative

Cytogenetics

NA

Molecular Studies

NGS and RNAseq work-up: Pending

Proposed Diagnosis

Mesentery:

Follicular dendritic cell sarcoma (FDCS) arising from precedent hyaline-vascular Castleman disease (HV-CD)

Interesting Feature(s)

A small subset of FDCS cases are reported to be associated with HV-CD , which can precede or co-occur with FDCS.

A hyperplasia–dysplasia–neoplasia model of FDC proliferation, as shown in this case, has been proposed for the link between HV-CD cases and FDCS.

Evidences have suggested that HV-CD might be a benign clonal neoplasm derived from lymph node stromal cells, possibly follicular dendritic cells.

EA4HP24-LYWS-213

Lymph node with simultaneous involvement by HHV8+ multicentric Castleman disease and Kaposi sarcoma

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Case Description

32-year-old male with past medical history of HIV, end-stage renal disease (status post deceased donor kidney transplantation), was admitted with pancytopenia, diarrhea and acute kidney injury. Sigmoidoscopy and concurrent colonic biopsy confirmed Kaposi sarcoma. Imaging studies revealed diffuse lymphadenopathy, splenomegaly and ascites. He underwent lymph node excision to rule out a possible lymphoproliferative disorder.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

The lymph node showed effacement of architecture by proliferation of vascular channels surrounded by an expansion of numerous plasma cells, some with large plasmablastic morphology, and scattered atretic follicles that are traversed by penetrating vessels. Also noted are multiple foci of slit-like vascular proliferations formed by spindled endothelial cells with minimal to moderate atypia.

Immunophenotype

Immunohistochemistry: Numerous CD138+ polytypic plasma cells with kappa and lambda expression are present. HHV8 stains scattered atypical large plasmablastic cells around atretic follicles that are negative for EBER(ish). Scattered EBER(ish)+ HHV8- cells are present in interfollicular areas. ERG highlights the atypical vascular channels, with diffuse HHV8 positivity in endothelial cells. The Ki-67 Proliferative index is 50% in interfollicular areas and 5% in other regions including vascular proliferations.

Flow cytometry: Plasma cells appear to be lambda biased by cytoplasmic light chain analysis, with a kappa:lambda ratio of 0.5 with no evidence of aberrant expression of CD56 or CD117. They appropriately express CD19, CD27, CD81, and CD38. There is a subpopulation of plasma cells that shows loss of CD27 and a kappa:lambda ratio of 0.29.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

- Kaposi sarcoma and HHV8+ Multicentric Castleman disease.
- Increased EBV+ lymphocytes, concerning for post-transplant lymphoproliferative disorder.

Interesting Feature(s)

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder while Kaposi sarcoma (KS) is a vascular tumor, both can be caused by HHV8 infection and have apparent predilection for HIV positive patients. While the two diagnoses are often made in different tissues, the coexistence of KS and MCD in the same tissue is less commonly reported. Although the exact association is unclear, it is hypothesized that due to lytic HHV8 infection of B-cells expose susceptible endothelial cells within the lymph nodes to high levels of HHV8 resulting in formation of KS islets in MCD lymph nodes. Lymph node involvement by KS is many times “microscopic” which may be subtle and can be missed on immunohistochemical staining. With our case, we wanted to highlight that MCD should be kept in mind as a differential diagnosis in a patient with KS, as identification of both diseases is crucial because the therapeutic targets may be different, and patients with untreated MCD are at higher risk of large B-cell lymphoma. Another interesting feature of our case that EBER(ish) shows increased EBV+ lymphoid cells within interfollicular areas that are negative for HHV8 which, in the context of known renal transplantation, may reflect and evolving post-transplant lymphoproliferative disorder.

EA4HP24-LYWS-217

Retroperitoneal Unicentric Castleman Disease, Hyaline Vascular Variant Associated With Thymoma: Are They Pathologically Related? The Old Link is Revive

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Case Description

Clinical information: A 49-year-old female. She presented with a history of chest tightness and intermittent coughing for a few weeks prior to the presentation. She

reported a history of iron deficiency anemia for 8 months. A retroperitoneal mass was discovered incidentally while doing an ultrasound abdomen for anemia investigation. She has a long-standing history of thyroid nodules.

Laboratory findings: Hemoglobin: 8.9 g/dL (normal range 11.3–15.2 g/dL), MCV: 87.9 fL (normal range 81–102 fL), WBC: 4.45 x10E9/L (normal range 3.4 to 10.1 X10E9/L), Platelets: 402 (normal range 150 to 450 X10E9/L), Iron: 10.2 mmol/l; ferritin: 74.6 mg/l , TIBC: 42.97 mmol/l ESR: 15 mm/h (normal <20 mm/h), CRP: 0.9 mg/dl (normal 0.8–1 mg/dl)

Radiology findings

Chest CT scan: There is a large anterior mediastinal partially calcified heterogeneously enhancing soft tissue lesion with few small cystic areas. It measures about 5.8 x 2.8 x 4.2 cm

No significant or abnormal-appearing neck lymph nodes.

Abdomena and pelvic CT scan: large left retroperitoneal soft tissue hypervascular mass measuring 8.5 x 7.5 x 10.5 cm.

Biopsy Fixation Details

Formalin-fixed and paraffin-embedded

Frozen Tissue Available

Not availbale.

Details of Microscopic Findings

The thymic mass microscopic findings: H&E sections show lobulated architecture with cellular lobules and intersecting fibrous bands. The neoplastic epithelial cells are forming clusters of polygonal cells admixed with various numbers of lymphocytes. Focally; the neoplastic cells are elongated with oval to spindle cell morphology with bland cytology.

The retroperitoneal mass microscopic findings: H&E sections show expansion of the paracortical area with proliferation of extensive vascular proliferation of high endothelial venules with perivascular hyalinization. Many atretic follicles were noted. Mantle zones are thickened with lymphocytes arranged in layers—the onion skin appearance.

Immunophenotype

- CD20 is positive in B-cell follicles with scattered B-cells in the interfollicular area.CD3 highlights the expanded paracortex with many positive small T-cells. CD21 highlights the convoluted follicular dendritic cell meshwork in the residual atrophic germinal centers. CD138 is positive in scattered, rare plasma cells. CD10 and BCL6 are positive in germinal centers, which are negative for BCL2. Negative IHC: IgG, IgG4, HHV-8 and EBER.

Cytogenetics

NA

Molecular Studies

B-cell clonality panel by PCR: Negative

Proposed Diagnosis

•The thymic mass: Thymoma, type AB (predominant B2 with fewer type A components).

Ø Pathologic Stage (pTNM, AJCC 8th Edition): pT1a, pN0

ØModied Masaoka Stage: Stage IIa

• The retroperitoneal mass: Consistent with unicentric Castleman disease, hyalin vascular variant.

Interesting Feature(s)

• Both thymoma and Castleman disease are extremely uncommon, and they are both linked to autoimmune or inflammatory disorders.

• The numerous associations between thymomas and other illnesses, such as autoimmune disorders, collagen vascular disorders, hematological disorders, neoplasia, and others, are well established.

•The medical condition that seems to have the strongest association with thymoma is myasthenia gravis. It is widely believed that thymomas are present in roughly 10–15% of myasthenia gravis (MG) patients.

•The association between Castleman disease and thymoma is not well established in the literature.

•Our patient has no underlying autoimmune disease, and it is still unclear if the patient's thymoma is the underlying cause of his retroperitoneal Castleman disease or if it is the other way around.

EA4HP24-LYWS-224

Unraveling Importance: Exploring a Rare Stroma-Rich Variant of Hyaline-Vascular Castleman Disease

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Case Description

36-year-old female who initially presented to an outside facility with abdominal pain. Imaging revealed a hyperdense retroperitoneal mass measuring 6.0 x 5.0 x 4.0 cm. A core needle biopsy led to a diagnosis of Castleman's disease, hyaline vascular type, oligocentric. Following four cycles of Rituxan without response, she was transferred to our facility for an exploratory laparotomy.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

H&E-stained sections reveal atrophic lymphoid follicles with hyalinized germinal centers and hyperplastic mantle zones, consistent with the typical morphology of hyaline-vascular type Castleman disease (HV-CD) lymphoid follicles. However, the bulk of the mass showed markedly expanded interfollicular zones containing a mixed population of small lymphocytes, increased vascularity, and a prominent spindled cell proliferation. These findings, along with immunohistochemistry, are indicative of an unusual stroma-rich variant of hyaline-vascular Castleman disease, also termed "angiomyoid proliferative

lesion." Importantly, no evidence of follicular dendritic cell (FDC) sarcoma or lymphoma was identified.

Immunophenotype

Positive findings include smooth muscle actin (SMA) expression in spindled cells, with a variable increase in vascularity confirmed by CD31, CD34, and factor VIII stains. However, the interfollicular area demonstrates negativity for Desmin, ALK, S100, HHV8, and EBV (EBER-ISH). Additionally, there is no evidence of extrafollicular expansion of follicular dendritic cells as indicated by negative CD21, CD23, or CD35 stains.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Castleman disease, hyaline-vascular type, stroma-rich variant (HV-CD)

Interesting Feature(s)

In this report, we present a rare stroma-rich variant of the hyaline-vascular type of Castleman disease, initially described by Danon et al. Some reports suggest that the underlying stromal cells in Castleman disease are clonally neoplastic and may originate from fibroblastic reticular cells (FRC) or follicular dendritic cells (FDC) due to their close clonal relationship. Additionally, there have been documented cases of malignant transformation of this variant in other studies. Therefore, it is crucial to approach this entity with increased caution when dealing with Castleman disease.

EA4HP24-LYWS-225

Features of KSHV/HHV8-associated multicentric Castleman disease in the setting of simultaneous widely metastatic Kaposi sarcoma

Dr. Briana Gibson[2,1]

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Case Description

The patient is a 38 year old Caucasian male with clinical history significant for uncontrolled HIV/AIDS (CD4 count 7), chronic hepatitis C, and known Kaposi sarcoma on the foot. He presented with diffuse lymphadenopathy above and below the diaphragm, splenomegaly, progressive lower extremity edema. A previous left inguinal lymph node excisional biopsy showed extensive metastatic Kaposi sarcoma (KS), leading to a diagnosis of lymphangitic KS. Because the lymph node was almost entirely replaced by KS, an additional specimen was obtained to rule out simultaneous hematologic malignancy/Castleman. This specimen

is a left level IV cervical lymph node excisional biopsy. After biopsy he continued to be symptomatic despite doxirubicin therapy with elevated IL-6 (41.87 pg/mL) and CRP (>240.00 mg/L), anemia, and anasarca with hypoalbuminemia.

Biopsy Fixation Details

Biopsy tissue was fixed in formalin and embedded in paraffin.

Frozen Tissue Available

None

Details of Microscopic Findings

Sections show several lymph nodes with varying degrees of infiltration by metastatic KS including some with complete effacement/possible nodular deposits of pure sarcomatous proliferation. Lymphoid tissue demonstrates follicles that vary in size from small, involuted forms to larger forms, with some rare concentric "onion-skinning" seen. Extensive mature plasmacytosis is present in the interfollicular areas, as well as some vascular proliferation and general lymphocyte depletion.

Immunophenotype

Immunostain for HHV8/LANA highlighted the extensive Kaposi proliferation as well as rare enlarged positive cells in the mantle zone of a few lymphoid follicles. In-situ hybridization for kappa/lambda showed polytypic distribution in plasma cells.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

KSHV/HHV8-associated multicentric Castleman disease with associated extensive metastatic Kaposi sarcoma

Interesting Feature(s)

The majority of cases of KSHV/HHV8-associated MCD occur in the setting of HIV and frequently co-occur with Kaposi sarcoma, but diagnosis in the setting of simultaneous HHV8+ neoplasm within the same tissue poses a diagnostic challenge. In this case the amount of simultaneous KS also left little residual lymphoid tissue for evaluation. The morphologic features of the case do not appear to clearly fufill the Fajgenbaum criteria (as applied to HHV8- cases), but the degree of plasmacytosis as well as clinical symptoms/findings do appear to support the diagnosis. Correlation with clinical and other laboratory findings is essential for evaluation.

EA4HP24-LYWS-235

Hyaline Vascular Variant of Castleman Disease Presenting as a Peri-Pancreatic Mass

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Case Description

The patient is a 37 year old female who presented with abdominal pain. A CT abdomen revealed a 5 cm peripancreatic mass and the patient was scheduled for diagnostic excision. Histologic sections revealed Castleman disease, hyaline vascular variant. The patient's imaging was negative for multicentric involvement, and she has continued with annual surveillance under Hematology-Oncology.

Biopsy Fixation Details

10% Formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Sections demonstrate an enlarged lymph node with distorted architecture. Abundant lymphoid follicles with abnormal germinal centers are present, characterized by two or more small germinal centers ("twinning"), irregularly shaped germinal centers, and lymphocyte depleted germinal centers. Focal areas demonstrate hyaline deposits and there are focal sclerotic blood vessels penetrating the germinal centers. Mantle zones show concentric rings of small lymphocytes. The interfollicular regions demonstrate areas with abundant blood vessels. Immunohistochemical stains show no aberrant antigen expression and no monoclonal populations. Concentric rings of follicular dendritic cells are highlighted by CD21 and CD23. HHV-8 and Cyclin D1 stains are negative. Kappa and lambda in situ hybridization shows polytypic expression of light chains. The proliferation index by Ki-67 shows a normal zonation pattern.

Immunophenotype

Flow cytometry revealed no aberrant or clonal population.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Hyaline Vascular Variant of Castleman Disease

Interesting Feature(s)

Unicentric Castleman disease frequently presents as an isolated mass in younger patients, is not associated with HHV-8 infection, and is typically asymptomatic. In a young patient

with a pancreatic or peripancreatic mass, lymphoproliferative disorders are an important diagnostic consideration with the differential diagnosis including IgG4-related disease. This case is a classic example of the presentation and histology of the hyaline vascular variant of Castleman disease.

EA4HP24-LYWS-245

Unicentric Castleman-disease

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Case Description

23-year-old man consulted for back pain for four months, which wakes him up at night. PET-CT scan: hypermetabolism associated with the paravertebral mass adjacent to D9, measuring 60x36x35 mm (SUVmax3.57), without the presence of hypermetabolic lesions in other locations. MRI does not show vertebral bone involvement, intracanal space-occupying lesions, or stenosis.

Complete resection of the paravertebral mass was performed. PET/CT was performed 6 months after diagnosis, with no evidence of pathological hypermetabolism, therefore no treatment was required. PET/CT study, last control three years after diagnosis, does not show lesions suggestive of relapse of the known lymphoproliferative process. Bilateral cervical hypermetabolic nodes with inflammatory characteristics; however, given the clinical history, evolutionary follow-up is decided.

Biopsy Fixation Details

10% buffered formalin fixed and paraffin-embedded.

Frozen Tissue Available

Not-available.

Details of Microscopic Findings

Encapsulated nodular lesion constituted by an increase in lymphoid follicles of variable size and contour. Alternation of atrophic and depleted germinal centers, showing an increase in follicular dendritic cells without dysplasia, with other hyperplastic germinal centers. Some germinal centers show hyalinized capillaries that penetrate them radially (“lollipop”), forming hyaline-vascular lesions. Expansion of the mantle area with lymphocytes that are arranged in concentric layers around the germinal center ("onion skin"), which sometimes contain two germinal centers ("twining"). Slight expansion of the interfollicular zone, observing proliferation of high endothelial venules with slight hyalinization, mature lymphocytes and very few plasma cells.

Immunophenotype

Germinal center lymphocytes show CD20+, CD79a+, CD10+, bcl-6+, and bcl-2-negative. Lymphocytes of the expanded marginal zone express bcl2+ and IgD+. The interfollicular

plasma cells are polytypic and T-lymphocytes do not show an aberrant immunophenotype, but show isolated TdT expression. KSHV/HHV8 latency-associated nuclear antigen (LANA) is negative. In situ hybridization for the Epstein Barr virus (EBER probe) is negative.

Cytogenetics

Not-done.

Molecular Studies

PCR: polyclonal immunoglobulin gene rearrangements (absence of a clonal B-cell population) with BIOMED-2 protocol.

Proposed Diagnosis

Unicentric Castleman-disease.

Interesting Feature(s)

Predominance of depleted germinal centers with exuberant hyaline-vascular lesions and isolated TdT cell expression.

EA4HP24-LYWS-249

Diagnosis of an Idiopathic Multicentric Castleman Disease – TAFRO case

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Case Description

We present the case of a 46-year-old female patient whose only relevant medical history is Graves' disease, currently being treated with normal thyroid function, and episodes of endometriosis that had undergone surgery on several occasions.

Prior to admission to our hospital, the patient reported two previous admissions in Ecuador for a condition compatible with left renal colic that required antibiotic treatment, lithotripsy, and a JJ catheter. Her condition worsened with the appearance of fever, edema and ascites of unknown cause, lymphadenopathy, and hepatomegaly. An exploratory laparotomy was even performed, which turned out to be white. Cultures and bone marrow aspirate (BMA) with flow cytometry study were negative. Progressive worsening of anasarca with deterioration of renal function, which was oriented as renal tubular necrosis. Treatment with corticosteroids is initiated. The patient requests voluntary discharge and returns to Spain.

Upon admission to our hospital, she presented with anasarca, moderate-large volume ascites, soft pitting edema, and hematomas without palpable lymphadenopathy. It presents as anasarca with hypoalbuminemia, cardiac and hepatic causes ruled out; thrombocytopenia (85000/mcL) and non-regenerative anemia (Hb89g/L, VCM89fL) with normal BMA; and acute kidney failure which became AKIN3 (peak creatinine 400mmol/L). During admission, cervical and supraclavicular lymphadenopathy, hepatomegaly, and bilateral pleural effusion were confirmed by imaging studies. Cultures and serological studies were negative. The initial suspicion is of lymphoproliferative disease versus other neoplasia. She starts treatment with corticosteroids.

Adenopathy resection was performed with a diagnosis of plasma cell variant Castleman's disease, which in the patient's context is compatible with idiopathic multicentric Castleman's disease - TAFRO (iMCD-TAFRO). Hemophagocytic syndrome was ruled out by BMA. She was transferred to the Clinical Hematology Department and started treatment with anti-IL6 monoclonal antibodies.

Biopsy Fixation Details

Formalin-fixed paraffin-embedded (FFPE) block.

Frozen Tissue Available

Yes

Details of Microscopic Findings

Lymph node with respected architecture with marked vascular proliferation, atrophy of the germinal centers, hyperplasia of dendritic cells (some with mild-moderate atypia), with “onion layers” appearance lymphocytes around the follicles and presence of abundant mature plasma cells around the follicles and in the paracortical area.

Immunophenotype

Negativity for HHV8, EBERs, no light chain restriction. IgG4/IgG ratio well below 40%.

Cytogenetics

Not performed.

Molecular Studies

Study of IgH (FR1, FR2 and FR3 region of the immunoglobulin heavy chain and kappa chain) and TCR beta and gamma polyclonal.

Proposed Diagnosis

Castleman disease, plasma cell variant. In the context of the patient, compatible with iMCD-TAFRO by meeting histological criteria, negativity for HHV8; major criteria (thrombocytopenia, anasarca, fever, and hepatomegaly) and minor criteria (mild hyperplasia of megakaryocytes in the BMA, elevation of alkaline phosphatase).

Interesting Feature(s)

The diagnosis of iMCD-TAFRO is complicated and rare, and in our case required admission to three different hospitals, showing an aggressive clinical course. It shows a histology compatible with the plasma cell variant, which is not the most common in cases of iMCD-TAFRO (mixed or hypervascular).

EA4HP24-LYWS-251

Castleman disease in 16-years-old female patient with cervical lymphadenopathy

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Medical Univeristy of Bialystok, of Medical Pathology, Bialystok, Poland

Case Description
16 year old female patient was admitted to the hospital with cervical lymphadenopathy, fewer, weight loss anf weakness.
CDR was eleveated.
Lymph node biopsy was done.
Biopsy Fixation Details
formallin fixed, parrafin embedded
Frozen Tissue Available
Yes
Details of Microscopic Findings
In the lymph node:
Atretic germinal centers traversed by sclerotic penetrating vessels and hyalinization - lollipop follicles
Mantle zones are thickened with lymphocytes arranged in layers - onion skin appearance
Follicular dendritic cells show proliferation
In the interfollicular areas, there is extensive vascular proliferation of high endothelial venules with perivascular hyalinization
Clusters of plasmacytoid dendritic
Plasma cells, immunoblasts and eosinophils are seen in the interfollicular areas
Unapparent sinuses and obliteration of the subcapsular sinuses are observed
Capsular thickening
Immunophenotype
CD20, CD10, Bcl-6, CD23 (+) in follicles
CD3, CD5, Bcl-2 (+) in T cells
MUM1, cyclinD1 (-)
Ki-67 (+)
EBV, HHV8 (-)
Cytogenetics
no
Molecular Studies
BRAF, JAK3 mutation
Proposed Diagnosis
Castleman disease hyaline vascular type

Interesting Feature(s)
Castleman disease is a rare enity in pediatric patients esspecially with inflammatory symptomes

EA4HP24-LYWS-255

A Case Report: HHV8 (+) Multicentric Castleman Disease

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Case Description
A 76-year-old female patient is admitted to hospital with history of fatigue, facial and left leg swelling for two months. B symptoms are absent. The physical examination revealed multiple palpable lymph nodes and hepatosplenomegaly. Anemia was found in her CBC. Other parameters were normal. The left axillary lymph node was excised for definite diagnosis.
Biopsy Fixation Details
The lymph node was fixated in %10 formaldeyde solution.
Frozen Tissue Available
There is no frozen tissue available.
Details of Microscopic Findings
The lymph node architecture is generally preserved. Concentric expansion of mantle zones, scattered plasmablasts in mantle zones, regressive changes in germinal centers and depletion of tingible body
macrophages in those germinal centers were observed. Also we noted increased vascularity, hyalinization and plasma cell sheets in the interfollicular area.
Immunophenotype
Immunohistochemistry revealed that CD20 positivity in follicles; CD3 (+) T cells in the interfollicular area; preserved FDC meshwork with CD23; negativity in germinal centers with bcl-2; expanded mantle zones with IgD; CD138 and MUM1 positivity and also lambda monotypic pattern in plasma cells. Plasmablasts were HHV8 positive. A few cells were EBER positive but it was thought that these cells were not plasmablasts.
Cytogenetics
None
Molecular Studies
None
Proposed Diagnosis
The final diagnosis is HHV8 (+) multicentric Castleman disease.

Interesting Feature(s)

This is a classic example of HHV8 positive multicentric Castleman disease. The interesting part of this case is that the patient responded very well to a single agent treatment. We also observed a small number of EBER positive cells, the significance of which is unknown.

EA4HP24-LYWS-257

2 Cases of POEMS-associated Multicentric Castleman Disease with Bone Marrow Involvement

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Case Description

We describe 2 cases of POEMS-associated multicentric Castleman disease (MCD) with bone marrow (BM) involvement.

Case 1 (C1): 65-year-old woman with 6 months of refractory ascites that began after COVID-19 vaccination.

- History: Raynaud phenomenon, renal insufficiency, hypothyroidism, polyneuropathy, leg edema, M-spike
- Labs:
  - 2 IgA λ M components with symmetric elevation of free light chains (FLC)
  - Serum IgA was elevated, predominantly IgA λ
  - VEGF >700 pg/mL
  - Lymph node (LN) and BM biopsies diagnostic of POEMS-associated MCD
- Imaging: Lymphadenopathy and splenomegaly
- Treatment: Daratumumab/lenalidomide for 1.5 years with clinical improvement and stable imaging findings

Case 2 (C2): 65-year-old man with several months of malaise, dyspnea, skin darkening, and peripheral neuropathy, also found to have hypothyroidism and hypogonadism, all reportedly after COVID-19 infection. Noted to have papilledema on routine ophthalmologic exam.

- History: Retinal vein occlusion treated with aflibercept
- Imaging: Pachymeningeal enhancement, lymphadenopathy, splenomegaly, osteosclerotic lesions
- Labs:
  - 2 IgA λ M components with elevated serum FLC in a normal ratio
  - Normal VEGF
- LN and BM biopsies confirmed POEMS-associated MCD
- Treatment: Daratumumab/lenalidomide with clinical improvement after 1.5 years; continues to have persistent disease on imaging

Biopsy Fixation Details

LN specimens: Separate blocks fixed in formalin and B-plus.

BM specimens: B-plus fixation followed by RapidCal Immuno decalcification.

Frozen Tissue Available

No

Details of Microscopic Findings

Both had LN biopsies diagnostic of plasma cell variant CD, including follicular hyperplasia with involuted germinal centers (GC), interfollicular hypervascularity, clusters of plasmacytoid dendritic cells (pDC), and aggregates of plasma cells (PC). C1 had characteristic mantle zone expansion with "onion skinning" and C2 displayed prominent sclerosis.

BM was normocellular (30-40%, C1) and hypercellular (70-80%, C2). Both cases had non-paratrabecular reactive lymphoid aggregates with plasmacytosis (C1: 10-15%, C2: 5-10%), often surrounding the lymphoid aggregates singly and in clusters (prominent in C2). In C2, megakaryocytes were mildly increased, occurring in loose clusters, including hyperlobated forms with bulbous nuclei/abnormally separated lobation.

Immunophenotype

In both LN, the reactive follicles were composed of small B cells (C1: PAX5+, C2: CD20+); C2 had GC (BCL6+, BCL2-) encompassed by CD21 follicular DC (FDC) meshworks. Both exhibited paracortical clusters of CD123+ pDC. Interfollicular CD138+ polytypic PC were present (C1: ISH, C2: IHC). In both, there was slight excess in IgA over IgG-expressing PC, with rare IgM in C2. HHV8 was negative in both.

Within the BM of both cases, lymphoid aggregates were composed of small CD20+ B cells with admixed CD3+ T cells. In C2, aggregates were associated with CD21+ FDC meshworks and GC were BCL6+, BCL2-. CD138+ PC demonstrated a slight excess of IgA over IgG, with a slight λ excess by IHC in C1, and polytypic in C2. Flow cytometry in C1 revealed a λ-restricted PC clone. There were occasional CD123+ pDC around lymphoid aggregates in C2.

Cytogenetics

Unremarkable by myeloma FISH panel

Molecular Studies

Unremarkable by myeloid- and lymphoid-targeted NGS panel

Proposed Diagnosis

POEMS-associated MCD

Interesting Feature(s)

BM involvement with somewhat unusual features

- C1: Monotypic λ PC; C2 did not have clear monoclonality
- C2: Features of CD in the bone marrow (CD123+ pDC)

Rare association with COVID-19 infection/vaccine

C2: Lack of elevation of serum VEGF on anti-VEGF therapy

EA4HP24-LYWS-258

Unusual Case of Castleman Disease, Plasma Cell Variant Involving Nasopharynx Having Monotypic Plasma Cells with Kappa Light Chain Restriction

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Case Description

A 38-year-old male known to have primary cutaneous marginal zone lymphoma diagnosed 5 months back. Currently presented with nasopharyngeal mass and clinical suspicion of lymphoma versus squamous cell carcinoma. CT scan imaging showed Lobulated left nasopharyngeal soft tissue enhanced mass measuring 1.9cm. No significant enlarged lymph nodes seen.

Blood testing showed normal range CBC.

Biopsy Fixation Details

The specimen was received in 10% formalin (fixed for 24 hours). It consists of multiple fragments of gray tan firm tissue with smooth outer surface measuring in aggregate 3.5 x 2.5 x 0.3 cm.

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic examination showed multiple fragments of nasopharyngeal tissue having scattered lymphoid follicles with variable size germinal centers (some are expanded and others are regressed) and thick mantle zones. Focally, there are follicles having multiple germinal centers sharing one expanded mantle zone. Between the follicles, there is a mix of lymphoid cells including small lymphocytes with round nuclei and condensed chromatin, many immunoblasts and sheets of mature appearing plasma cells. In addition, prominent blood vessels are seen in the interfollicular area.

Immunophenotype

On immunostaining, the small lymphoid cells in the interfollicular area show a mix of T-cells and B-cells. The B-cells are positive for CD20, PAX-5 and BCL2 and negative for CD3, CD5, CD10, BCL6, MUM1, IgD, CD21, CD23, and cyclin D1. The immunoblasts show expression of CD20, PAX-5 and CD30. The plasma cells are abundant and show expression of CD38, CD138, MUM1 and kappa, and negative for lambda and cyclin D1. Ki-67 is expressed by around 25% of cells. CD23 and CD21 highlight expanded FDC meshwork in the background of the follicles. Staining for HHV-8 is negative. The expanded mantle zones are positive for IgD and showed dim positivity for CD5, however cyclin D1 is negative.

Cytogenetics
Not performed
Molecular Studies
Not performed
Proposed Diagnosis
Unicentric Castleman disease, plasma cell variant, kappa restricted.
Interesting Feature(s)
This is a challenging case, the differential diagnosis is between Castleman disease, plasma cell variant, and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). The presence of expanded follicles containing multiple germinal centers that share thick mantle zone, and increased interfollicular plasma cells with prominent blood vessels favor Castleman disease.

EA4HP24-LYWS-260

Follicular Dendritic Cell Sarcoma Arising from a Background of Castleman Disease, Hyaline-Vascular Variant

Dr. Ozgur Can Eren, Dr. Ting Zhou, **Prof. Ahmet Dogan**

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Case Description
A 60-year-old female patient, diagnosed with endometrial cancer (T1bN0Mx) in September 2022, with recurrence in February 2023 (under radiation therapy). Chest CT in June 2023 demonstrated a 4.7x3.6x5.2 cm heterogenous right paratracheal mass and a stable 1.1 cm nodule within posterior left upper lobe. The paratracheal mass was biopsied in July 2023 with clinical suspicion of non-small cell lung cancer. Slides were submitted to MSK for second opinion in August 2023.
Biopsy Fixation Details
Received fresh. Touch preps (air-dried smears) are made, and representative tissue is placed (RPMI) for flow cytometry & cytogenetic studies. The remainder of the tissue is fixed in formalin.
Frozen Tissue Available
Frozen section diagnosis was: “Lesional tissue. Differential diagnosis includes lymphoproliferative disorder vs thymoma. Flow and cytogenetics submitted.”
Details of Microscopic Findings
Representative blocks demonstrate two distinct areas, compatible with:
Follicular dendritic cell sarcoma (part I)

- The tumor demonstrates a diffuse proliferation of spindled to ovoid cells with a storiform, fascicular, or whorled growth pattern. Small lymphocytes are seen, infiltrating tumor cells.
- Tumor cells are medium to large; have moderate amounts of eosinophilic cytoplasm with indistinct cell borders creating a syncytial appearance. Nuclei are elongated, with delicate nuclear membrane, vesicular chromatin and small but distinct nucleoli. Binucleate and multinucleate forms are observed, reminiscent of benign FDCs.

Hyaline-vascular Castleman disease (part II)

- Areas of lymphoid follicles with regressed germinal centers, eosinophilic hyaline material deposition and onion-skinning.

Immunophenotype

- Positive: CD21 (strong), CD35 (diffuse), Fascin (equivocal, subset), CXCL13, clusterin, MNDA
- Negative: AE1/AE3, CAM5.2, P40, CD23, CD163, CD68, desmin, myogenin, muramidase, calretinin, OCT2, BOB1, PD1, CD25, CD2, CD3, CD5, CD7, CD20, PAX5, CD10, BCL6, CD8, MUM1 CyclinD1, EBV-encoded RNAs (EBERs) ISH, CD30, CD1a, ALK1, EMA, D240, CD34, CD15, CD56, HMB45, CD43, TdT, CD4, S100.
- Flow cytometry: The lymphocyte immunophenotypic findings show no diagnostic abnormalities.

Cytogenetics

Not reported.

Molecular Studies

B-Cell and T-Cell Gene Rearrangements were assessed via IgH, IgK and TCR-gamma; all turned out negative.

Proposed Diagnosis

Follicular dendritic cell sarcoma arising from a background of Castleman disease, hyaline-vascular variant.

Interesting Feature(s)

HV-Castleman disease might represent a clonal process, likely driven by stromal elements such as FDCs (PMID: 10843293, 11979097, 24201121).

- FDC sarcoma might arise from abnormal, dysplastic FDCs frequently seen in HV-Castleman disease
- Although the underlying pathogenesis is not completely understood, absence of EBV infection suggests an alternative mechanism of neoplastic transformation.
- FDC sarcoma is a rare, yet significant condition.
- This case offers a comprehensive examination of the morphological and immunophenotypic features, thereby facilitating the accurate diagnosis of this challenging disease.

EA4HP24-LYWS-261

Castleman Disease, Plasma Cell Variant, with IgA Lambda Restricted Plasma Cells, Associated with Underlying Plasma Cell Neoplasm

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Memorial Sloan Kettering Cancer Center, Hematopathology Service, NYC, USA

Case Description

A 59-year-old male with a lump in the left groin. The lump was first noticed in late-2019 and was not complicated by any systemic symptoms. Excisional biopsy showed Castleman disease, plasma cell variant (07/2020). PET scan demonstrated involvement in left pelvic & inguinal nodes (08/2020). Due to unresectable disease, the patient received 4 doses of rituximab without any response (11/2020). Slides were submitted to MSK for second opinion (06/2021).

Biopsy Fixation Details

Unknown.

Frozen Tissue Available

No.

Details of Microscopic Findings

- Lymph node with partially obliterated sinuses, numerous follicles showing expanded mantle zones with concentric ring (onion skin) morphology and regressed germinal centers with hypervascularity occasionally traversing through the atrophic follicles.
- Small plasma cell aggregates and clusters of plasmacytoid dendritic cells are seen.

Immunophenotype

- CD20 shows B-cells with a nodular distribution. Residual germinal centers have weak CD10, high Ki67 and no BCL2 staining. CD3/CD5 show T-cells in the interfollicular areas.
- CD138 highlights dense collections with λ immunoglobulin light chain predominance (in situ hybridization). The plasma cells are a mixture of IgA and IgG. The IgA(+) plasma cells correspond to the λ-restricted plasma cells. IgG4 highlights scattered cells and IgD highlights mantle zones. Cyclin D1 highlights few cells.
- IgM, OSCAR, HHV-8, T.pallidum, EBER-ISH are negative.
- Flow cytometry (per report): B-cells (36%) appear polytypic with a normal k/λ ratio (1.2). T-cells (58%) show no pan T-cell antigenic loss, nor CD4/CD8 subset restriction.

Cytogenetics

Not reported.

Molecular Studies

No clonal rearrangement involving the Ig Heavy chain was detected.

Proposed Diagnosis Castleman disease, plasma cell variant, with IgA lambda restricted plasma cells. Associated with underlying plasma cell neoplasm.

Follow up:

Serum free light chain test (06/2021): Kappa: 2.73 [0.3-1.9], Lambda: 4.14 [0.5-2.6], k/λ ratio: 0.66 [0.3-1.7]

Immunofixation interpretation (06/2021): IgA λ monoclonal gammopathy

Bone marrow evaluation (07/2021):

- Cellular marrow (~30% cellularity) with trilineage maturing hematopoiesis and no increase in blasts.
- Scattered and focally clustered plasma cells with no cytologic atypia, constitute <5% of marrow cellularity (CD138/MUM1) and appear to be predominantly IgA & λ restricted.

Flow Cytometry: Abnormal plasma cell population (1.7% of total WBC, 53.9% of total plasma cells):

- CD19 (absent), CD20 (subset), CD27 (absent to dim), CD45 (absent), CD56 (subset), CD81 (subset absent), CD117 (subset), and monoclonal λ cytoplasmic light chain restriction; with normal expression of CD38, CD138, CD229, CD319.
- No abnormal B/T/myeloid population was detected.

Clinical & Radiologic Evaluation: No evidence of (Poly)neuropathy, Organomegaly, Endocrinopathy or Skin changes.

Interesting Feature(s)

Although histological features of the lymph node is typical for PCV-Castleman disease; clonal plasma cells in the LN and presence of a systemic plasma cell neoplasm raises the following questions:

- Should this case be considered as a ***LN-based plasmacytoma*** rather than CD-PCV?
- With IgA/λ restriction in LN, IgA/λ monoclonal gammopathy and a small plasma cell clone in BM, should it be considered within the spectrum of ***POEMS syndrome***?
- Should CD-PCV associated with monotypic plasma cells be considered ***LN manifestation of plasma cell neoplasms*** rather than a distinct entity?

EA4HP24-LYWS-271

Unicentric Castleman disease, hyaline vascular subtype, with prominent follicular dendritic cell proliferation in a peripancreatic mass

Dr. Lisa D. Yuen, Dr. Abner Louissaint

Massachusetts General Hospital, Pathology, Boston, USA

Case Description

A 53-year-old man presented for an incidentally discovered 6.5 x 5.7 x 3.2 cm peripancreatic mass arising along the posterior pancreatic head. He had 16 pounds weight loss over 2 years, but no changes in appetite, bowel movements, pancreatic function, fevers, night sweats, or adenopathy. A peripheral blood count was normal. Fine needle aspiration biopsy

showed polymorphous small lymphocytes and no malignant cells. Similar findings were seen on repeat FNA biopsy one month later. Due to continued suspicion for a pancreatic malignancy, the patient underwent a pancreatoduodenectomy (Whipple) procedure with hepatic artery and periportal lymph node excision. Gross examination of the specimen revealed a well-circumscribed, pink-tan, solid mass with a vaguely nodular cut surface. The mass abutted but did not extend into the pancreatic parenchyma and bowel wall. After a diagnosis was established, the patient required no further therapy and has been disease-free for 10 months.

Biopsy Fixation Details

FFPE of the Whipple specimen including peripancreatic lymph nodes

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the peripancreatic mass show lymph node tissue comprised of a dense proliferation of anastomosing follicles with serpiginous architecture, and mostly small mature lymphocytes with round nuclei and condensed chromatin. There are occasional atrophic germinal centers within the follicles. There is prominent vasculature with clusters of plasma cells around the vessels. The lymph nodes from the attached peripancreatic adipose tissue show follicular hyperplasia with atretic germinal centers, expanded concentric layers of the mantle zone, and sclerotic penetrating vessels. The excised hepatic artery and periportal lymph nodes showed only sinus histiocytosis.

Immunophenotype

Immunohistochemical stains show that the numerous follicles in the mass are comprised mostly of small CD20+ PAX5+ B cells and are invested within dense CD21+ CD35+ FDC meshworks. The B cells co-express BCL2 and are negative for CD5, CD43, cyclin D1, SOX11, CD30, and TdT. CD10 and BCL6 highlight cells in scattered small atrophic germinal centers. Ki67 shows a proliferation index of approximately 5-10% outside of germinal centers. There are thin rims of small CD3+ CD5+ T cells outside of follicles. A stain for MUM1 highlights plasma cells clustered around vessels, which are polytypic by kappa and lambda stains. CD123 stains scattered plasmacytoid dendritic cells. A special stain for HHV-8 and in situ hybridization for EBER are negative.

Flow cytometry performed on the peripancreatic mass showed no evidence for a monoclonal B-cell or unusual T-cell population.

Cytogenetics

46,XY[15]

Molecular Studies

Not performed

Proposed Diagnosis

Unicentric Castleman disease (CD), hyaline vascular subtype

Interesting Feature(s)

The patient's presentation of a large peripancreatic mass was clinically concerning for a primary pancreatic or duodenal malignancy. Retroperitoneal CD is rare and has been reported in case reports. The patient had undergone two prior nondiagnostic FNA biopsies; a diagnosis of CD requires an excision or resection specimen. The prominent FDC

meshwork proliferation raised the possibility of follicular dendritic cell sarcoma. However, the lack of cytologic atypia, relatively few spindled cells in comparison to lymphocytes, low Ki67 proliferation index, and normal karyotype are reassuring. The morphologic spectrum of CD is highlighted in this case by the anastomosing serpiginous follicles in the main mass, contrasted with the numerous atretic follicles seen in the peripancreatic retroperitoneal lymph nodes.

EA4HP24-LYWS-275

Idiopathic Multicentric Castleman disease (iMCD)-TAFRO variant, diagnosed in the bone marrow

Dr. Dorottya I. Laczko[1], Dr. Vinodh Pillai[2], Dr. Olga Pozdnyakova[1]

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Case Description

10-year-old female with no significant past medical history who presented with a prolonged febrile illness progressing to shock and multisystem organ failure of unknown etiology. Extensive infectious and rheumatologic work-up was negative. Her laboratory findings were notable for persistent leukocytosis with neutrophilia and lymphopenia, anemia and thrombocytopenia. Imaging studies showed enlarged cervical and axillary lymph nodes, hepatosplenomegaly, ascites and anasarca. Immunologic studies showed elevated IL-6, IL-8, IL-10 and TNF-α levels. She underwent bone marrow biopsy to rule out an underlying myeloproliferative disorder.

Biopsy Fixation Details

Bone marrow core biopsy: fixed in zinc formalin, decalcified in formical.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Bone marrow aspirate: Markedly increased number of megakaryocytes in spicules with frequent atypical hyperlobated forms. Blasts are not increased. Erythroid and myeloid elements show orderly maturation without cytologic atypia

Bone marrow biopsy: Markedly hypercellular marrow with increased atypical hyperlobated megakaryocytes that are focally in aggregates. Dysplastic features or tight clustering are not seen. Dilated sinuses with intrasinusoidal hematopoiesis are noted. Reticulin stain shows grade 1 fibrosis

Immunophenotype

Immunohistochemistry: CD34 highlights rare scattered blasts and dilated sinuses. CD42b shows increased number of atypical megakaryocytes.

Cytogenetics

Normal female karyotype: 46,XX[20]

FISH studies: negative for *BCR:ABL1* rearrangements.

Molecular Studies

Next Generation Sequencing Studies:

- No clinically significant (Tier 1 or Tier 2) sequence variants or fusions were identified
- One copy number variant with potential clinical significance (Tier 2) in *NOTCH1* gene
- Four sequence variants of uncertain significance (Tier 3) in *CCND3, CDKN2B, KMT2A* and *TET2* genes

Genome wide single nucleotide polymorphism (SNP) microarray analysis

Gain of chromosome 9q34.3 involving part of the *SEC16A* and *NOTCH1* genes at low-level mosaicism (~20% of cells).

Proposed Diagnosis

TAFRO variant of idiopathic Multicentric Castleman disease (iMCD)

Interesting Feature(s)

iMCD is a rare lymphoproliferative disorder with characteristic lymph node morphology. TAFRO syndrome is defined by the presence of thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly and can be seen with iMCD or as an isolated process without iMCD. To date, there is no clear guidance on treatment of TAFRO in the absence of definitive diagnosis of iMCD, leading to suboptimal management and high morbidity, although differentiation of iMCD-TAFRO from TAFRO syndrome is essential due to differences in the therapeutic approach and its high mortality. The final diagnosis of iMCD-TAFRO can be hampered by the lack of diagnostic lymph node histology as a subset of patients with TAFRO syndrome do not show apparent lymphadenopathy, therefore can be easily missed. In addition, the critical condition of TAFRO patients can further preclude a concurrent lymph node sampling, while prompt treatment in these cases would be essential. In such cases, Masaki's diagnostic criteria should be considered that requires 3 major (anasarca, thrombocytopenia, systemic inflammation) and 2 minor criteria of iMCD-TAFRO, but does not require lymph node biopsy. In our case, following exclusion of a myeloproliferative disorder (*BCR-ABL, JAK2, CALR* were negative) or an infectious/autoimmune disease the patient was treated with siltuximab with significant clinical improvement.

EA4HP24-LYWS-281

KSHV/HHV-8-associated multicentric Castleman Disease in an HIV+ individual.

Dr. Fernando Alekos Ocampo Gonzalez, Amy Ku, Murty Vundavalli, Wen-Hsuan Wendy Lin, Rebecca Leeman-Neill, Craig Soderquist, Bachir Alobeid, Govind Bhagat

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Case Description

A 46-year-old HIV+ male on HAART therapy (bectegravir-emtricitabine-tenofovir) with h/o Kaposi sarcoma of the left lower extremity (status post chemotherapy) presented to our institution with persistent cough, fever, chills, diffuse body aches and a 20 lb. weight loss. Physical examination revealed bilateral cervical, supraclavicular, axillary and inguinal lymphadenopathy (LAD). CT of chest/abdomen/pelvis revealed a cavitary lesion in the right upper lobe of lung, hepatosplenomegaly and generalized LAD. CBC showed WBC count - 10.53 x 10^3u/L, Hb - 9.2 g/dL, and Hct - 30.3%. C-reactive protein level and erythrocyte sedimentation rate were elevated, a QuantiFERON test for TB was negative, HIV viral load was 23 copies/mL, EBV quantitative PCR was 461 IU/mL, and blood culture was positive for MRSA. An axillary lymph node (LN) biopsy revealed KSHV/HHV-8-associated Castleman disease (CD). The patient was started on rituximab therapy, which is currently ongoing.

Biopsy Fixation Details

The biopsy was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

Sections of the LN showed altered nodal architecture. The lymphoid follicles displayed a morphologic spectrum, ranging from follicular hyperplasia to follicular fusion with twinning of germinal centers, to regressive transformation (burnt-out follicles), and prominent, penetrating blood vessels ('lollipop sign'). The surrounding mantle zones exhibited an 'onion skin' appearance. Scattered, large plasmablasts were seen at the interface of the germinal centers and mantle zones and within the mantle zones. The paracortical areas showed lymphocyte depletion, increased vascularity and prominent plasmacytosis. Sinuses were not visualized.

Immunophenotype

The lymphoid follicles (CD20+, CD79a+, PAX5+, CD19+) showed reactive germinal centers (CD10+, BCL6+, BCL2-), associated with dense follicular dendritic cell meshworks (CD21+, CD23+). Reduced numbers of T-cells (CD3+, CD5+) were seen in the paracortical areas and the plasma cells in this location were polytypic by kappa and lambda ISH (kappa:lambda - 2:1). ISH for EBER was negative. Stains for Ig heavy chains showed a predominance of IgG+ plasma cells in the interfollicular areas and only rare IgG4+ plasma cells.

The follicular/mantle zone plasmablasts were MUM1+, Cyclin D1-, CD138-, IgM+, lambda+, C-MYC+/-, and HHV8/LANA+. No HHV8+ vascular/spindle cell proliferation was seen.

Cytogenetics

Normal male karyotype. Clonal chromosomal abnormalities were not detected.

Molecular Studies

IGH and TCR gene rearrangement analysis by fluorescent PCR showed polyclonal products.

Proposed Diagnosis

KSHV/HHV-8-Associated multicentric Castleman disease.

Interesting Feature(s)

This case demonstrates classic morphologic and immunophenotypic features of KSHV/HHV8-associated multicentric CD. However, HHV8/LANA+ plasmablasts were infrequent, seemingly accounting for only a subset of the IgM+ plasmablasts. The frequency and distribution of follicular/mantle zone plasmablasts can be quite variable in HHV8/KSHV-associated CD. Hence, it is crucial to evaluate several markers for plasmablasts by immunohistochemistry (MUM1, Ig light chains, and IgM) along with HHV8/LANA in suspected CD cases for appropriate diagnosis/classification.

EA4HP24-LYWS-282

KSHV/HHV8-associated multicentric Castleman Disease and nodal Kaposi sarcoma displaying a lymphangiectatic pattern in an HIV+ individual.

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Case Description

A 30-year-old HIV+ male, poorly compliant to HAART therapy, presented to our institution with diarrhea, fever, chills, night sweats, and generalized lymphadenopathy (LAD). Pertinent labs included a CBC showing normal WBC count, Hb 7.5 g/dL, relative lymphocytosis (40%) and monocytosis (13%); CD4 count - 141/mm^3; HIV viral load - 78,900 copies/mL, and EBV DNA - 364 IU/mL. The HHV-8 viral load was elevated (21,200 copies/mL). An axillary lymph node (LN) biopsy revealed concurrent KSHV/HHV8-associated Castleman disease (CD) and Kaposi sarcoma (KS). Antiretroviral medications were restarted, and the patient was treated with rituximab and doxorubicin. PET/CT after 12-months showed significant decrease in LN size and normalization of metabolic activity.

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

The LN showed a spectrum of follicular changes, including follicular hyperplasia, fusion/twinning of germinal centers, and atrophy with variable depletion of germinal center cells and prominent hyalinized penetrating blood vessels, and mantle zone hyperplasia. Some follicles had dystrophic follicular dendritic cells (FDCs). Scattered plasmablasts were seen at the edges of the germinal centers and within the mantle zones. The interfollicular areas showed increased vascularity, lymphocyte depletion and plasmacytosis. A spindle cell proliferation was seen surrounding a few lymphoid follicles, and a separate focus of thin walled, dilated lymphatic spaces, lined by bland, flattened endothelial cells with intraluminal proteinaceous material, was noted.

Immunophenotype

The lymphoid follicles were composed of B-cells (CD20+, CD79a+, PAX5+) with reactive germinal centers (CD10+, BCL6+, and BCL2-) and expanded mantle zones (IgD+), associated with dense FDC meshworks (CD21+, CD23+). The follicular/mantle zone plasmablasts had the following phenotype: MUM1+, CD138-, lambda+, IgM+, and HHV8/LANA+. MUM1 and CD138 showed increased plasma cells within the interfollicular areas, which were polytypic by ISH for kappa and lambda mRNA (kappa:lambda - 2:1). Most of the plasma cells were IgG+, only rare IgG4+ plasma cells were seen. Reduced numbers of small-sized mature T-cells (CD3+, CD5+) were present within the paracortical areas, but scattered and small, loose collections of TdT+ lymphocytes were seen in this location. ISH for EBER mRNA showed a few scattered small-sized EBER+ lymphocytes.

The spindle cell proliferation was CD34+, ERG+ and HHV8/LANA+. The focus of dilated thin-walled vessels was D2-40(weak)+, CD31+, FLI-1+, ERG+, and CD34+/- and HHV8/LANA+.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

KSHV/HHV8-associated multicentric Castleman disease and nodal Kaposi sarcoma.

Interesting Feature(s)

The presence of KS in patients with KSHV/HHV8-associated-CD is not uncommon, however isolated nodal KS is rare. LN involvement by KS can be subtle, as exemplified by the current case, which showed a focal spindle cell proliferation with typical KS morphology and an unusual and rare morphologic variant of KS (lymphangiectatic) in another area. The latter pattern, which has been described at cutaneous and mucosal sites does not show typical KS morphology, but the cells express D2-40, CD34, CD31, and HHV8/LANA.

Variable numbers of TdT+ lymphocytes lacking morphologic atypia can be seen within the paracortex in all types of CD, most commonly in the hyaline vascular variant. The TdT+ lymphocytes in our case focally showed a tumor infiltrating lymphocyte (TIL)-like pattern, but the density did not reach the threshold for an indolent T-lymphoblastic proliferation.

EA4HP24-LYWS-300

KSHV/HHV8-associated multicentric Castleman disease and Kaposi sarcoma in a same lymph node.

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Hospices Civils de Lyon, Pathology, Pierre Bénite, France

Case Description

A 65-year-old man presented with fever, asthenia and weight loss. Scanner showed a polyadenopathy without hepatosplenomegaly. Polyclonal hypergammaglobulinemia was present. The patient was treated in dermatology for almost 20 years for a non-HIV-positive African Kaposi cutaneous sarcoma, with various therapies, most recently pegylated liposomal doxorubicin (Caelyx) six years earlier. Since then, his Kaposi sarcoma has been in complete remission. An inguinal lymph node biopsy was performed, measuring 3 × 2 × 1 cm.

Biopsy Fixation Details

Neutral buffered formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

The architecture of the lymph node was preserved. The lymphoid follicles showed germinal centres of variable size, with some regressive germinal centers and follicular dendritic cells prominence. In the interfollicular areas, there was vascular and plasma cell hyperplasia.

On a cross-section (slide D), there was an intra- and subcapsular proliferation of spindle cells with numerous red blood cells, suggestive of Kaposi sarcoma.

Immunophenotype

There was a preserved distribution of B and T zones. The anti-CD20 antibody confirmed the regressive nature of some germinal centres. The anti-CD23 antibody highlighted an hyperplastic network of follicular dendritic cells, sometimes with an "onion bulb" appearance. The anti-MUM1 antibody confirmed the presence of numerous polytypic plasma cells. The LNA1 anti-HHV8 (Human Herpes Virus) antibody highlighted a few cells in the mantle zones and in the interfollicular areas. Eber RNA *in situ* hybridization was negative.

The spindle cells expressed vascular markers (CD31, CD34 and ERG) and LNA1 protein of HHV8, in favour of a focus of Kaposi sarcoma, which measured 3 mm on histological section.

Cytogenetics

No

Molecular Studies

There was no immunoglobulin nor T-cell receptor gene rearrangement (BIOMED-2).

Proposed Diagnosis

KSHV/HHV8-associated multicentric Castleman disease and a subcapsular focus (3 mm) of Kaposi sarcoma.

Interesting Feature(s)

Foci of Kaposi sarcoma can be associated with KSHV/HHV8-associated multicentric Castleman disease in a lymph node. Foci of kaposi sarcoma can be small and difficult to identify. Nevertheless, it is important to detect this association, which can have an impact on treatment. Indeed, some cases of Kaposi sarcoma have been described which flared up under treatment with rituximab or corticosteroids.

EA4HP24-LYWS-309

HHV8-associated multicentric Castleman disease with concomitant Kaposi sarcoma and disseminated histoplasmosis

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Case Description

The patient was a 47-year-old male with 6-year history of untreated HIV infection (CD4 <10 cells/mL, Viral load 91200 copies/mL) who presented to the hospital with 1-month history of fever, chills, night sweats, and unintentional weight loss. Physical exam revealed diffuse palpable lymphadenopathy and purple confluent, annular lesions on the extremities, consistent with plaque-stage Kaposi sarcoma on biopsy. Histoplasma urine antigen was positive. CT chest and abdomen revealed multiple enlarged lymph nodes (measuring up to 27 mm), concerning for a lymphoproliferative disorder. An axillary lymph node excisional biopsy was recommended for further evaluation.

Biopsy Fixation Details

The axillary lymph node specimen was freshly submitted and measured 4.6 x 3.8 x 1.1 cm in aggregate. Representative sections of the largest lymph node were submitted for flow cytometry and cytogenetic studies. The remaining tissue was submitted in formalin and paraffin-embedded.

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections reveal lymph node tissue with distorted nodal architecture that includes regressed/atrophic hyalinized follicles, lymphocyte-depleted follicles and interfollicular zones, and poorly formed non-caseating granulomas associated with intracellular yeast with narrow-based budding, most consistent with *Histoplasma* spp. The interfollicular zones contain increased mature-appearing plasma cells. Few intermediate to large atypical plasmablast-like cells are seen in mantle zones of regressed follicles. There are multifocal irregular vascular structures with atypical spindled endothelial cells that are associated with red blood cell extravasation and siderophages. Sheets of large, transformed

cells are not identified. Diagnostic Reed-Sternberg cells and Reed-Sternberg cell variants are not identified.

Immunophenotype

Immunohistochemistry/special stains: CD3 highlights scattered interfollicular T cells. CD20 and PAX5 highlight small B cells, mainly in a follicular distribution. CD21 highlights follicular dendritic meshworks associated with residual follicles. The plasmablast-like cells co-express HHV8 (LANA), MUM1, are lambda light chain restricted (ISH), and lack expression of CD20, PAX5, CD138, and EBV (EBER probe). Kappa and lambda light chain ISH also highlight increased polytypic plasma cells that co-express CD138 and MUM1. The abnormal spindled endothelial cells are HHV8 (LANA) positive. GMS highlights intracellular yeast forms that lack mucicarmine, consistent with *Histoplasma* spp. AFB stain is negative.

Flow cytometry: A limited panel was performed due to paucicellularity of the specimen. The findings provided no immunophenotypic evidence of a non-Hodgkin B cell lymphoma.

Cytogenetics

Conventional cytogenetic studies could not be performed due to failure to yield metaphase cells.

Molecular Studies

Not performed on this specimen.

Proposed Diagnosis

HHV8-associated Multicentric Castleman Disease in the background of Kaposi sarcoma and Histoplasmosis.

Interesting Feature(s)

This represents a case of HHV8-associated multicentric Castleman disease (MCD) with classic clinical presentation in the setting of untreated HIV infection. The morphologic features of HHV8-MCD are present, but obscured by prominent nodal involvement by Kaposi sarcoma and disseminated histoplasmosis, which may lead to a missed diagnosis of MCD. Careful attention to MCD-associated morphologic features prompted more extensive immunohistologic examination for HHV8-associated disease and cinched the diagnosis.

EA4HP24-LYWS-312

IgG4-related disease overlapping with an early hyaline Castleman disease

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Case Description

85 year old woman with persistent enlarged axillary lymphadenopathy and type 1 diabetes mellitus, otherwise well.

The largest lymph node biopsy in May 2020 showed mild follicular hyperplasia and paracortex expansion by mixed population of cells. The features were not explaining her lymphadenopathy. In October 2020 the largest lymph node (50 mm) was excised.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Paracortical hyperplasia with some vascular proliferation, polymorphous cell infiltrate, including easily identifiable eosinophils and moderate number of plasma cells. Heavily skewed CD4/CD8 ratio in favour of helper T-cells, although no expansion of FDC meshworks, no increase in proliferation fraction of T-cells and no EBV-expressing cells. No large atypical cells of Reed-Sternberg/Hodgkin morphology seen, although some larger CD30(+) CD15(-) immunoblast-like celle were observed in modest numbers.

B-cell component showed florid follicular hyperplasia in many, but not all follicles, with numerous secondary reactive follicles with evident germinal centre zonation, highlighted by CD20, CD79a, BCL6, CD10, BCL2(-) with peserved FDC meshworks on CD21 and CD23 in many follicles. An occasional follicle showed strong CD10 expression, but was BCL2(-) with zonation evident on ki67.

Some follicles appeared minituarised, the other revealed variable degree of germinal centre atrophy with an occasional vascular channel penetration and some hyalinisation/oesinophilic matrix deposition, associated with subtle "onion-skinning"-like change in mantle zones.

Several adjacent sets of follicles showed joining up of FDC meshworks with apparent confluence of germinal centres in an occasional set, where FDC meshworks showed figure of eight and targetoid configuration.

An occasional perifollicular microgranulomata were observed. Small well-formed conventional epitheliod granuloma without necrosis was also seen

Pasma cells were not abundant, but the majority were positve for IgG, of which over 50% expressed IgG4.

Immunophenotype
Paracortex expansion by CD3/CD4/CD5(+) T-cells and follicular hyperplasia (CD10/BCL6(+) BCL2(-), supported by ki67-zonations) with some follicles showing atrophy and confluence.
Polytypical plasma cells on light chain immunohistochemistry.
IgG(+) plasma cells with over 50% IgG4(+) cells
EBER, HHV8, AE1/3 - negative.
Cytogenetics
Not done
Molecular Studies
PCR was negative for clonal heavy/light chain or clonal TCR beta-gamma expansion.
Proposed Diagnosis
IgG4-related disease overlapping with an early hyaline Castleman disease
Interesting Feature(s)
Clinically and histologically challenging diagnosis.
Samples collected 4 years ago. Patient did not receive treatment. Recent PET scan shows similar findings to 2020 of "non-specific" significant lymphadenopathy without evidence of inflammatory traits. Her serum IgG4 was 1.66 g/l in 2021 and 2.36 g/l in 2023.
Histologically subtle features. Range of secondary follicle change, predominantly prominent reactive follicular hyperplasia, but also atrophic follicles with hyalinised vascular penetrations and focally FDC confluence and "onion-skinning".
Paracortical expansion by polymorphous cell infiltrate with dominance of CD4(+) T-helper cells, moderate number of plasma cells and focally numerous eosinophils.
Several perifolicular microgranulomas, described in the literature as a feature of IgG4-reated sclerosing disease.
IgG4(+) plasma cells exceeded 50% of IgG(+) plasma cells. Most plasma cells were IgG(+).

EA4HP24-LYWS-316

Atypical IgG4+ Lymph-node Plasmacytic Proliferation

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Case Description
An 88-year-old male Italian patient presented to the hematology outpatient clinic because of low platelet count. His past medical history includes chronic kidney failure due to nephrectomy performed for renal cancer, essential hypertension and chronic respiratory failure after Sars-COV-2 infection. The patient was in decent clinical conditions with no

symptoms reported. Blood examinations resulted in: WBC 5620/mmc (N 64%, L 22%), Hb 13.1 g/dl, MCV 96 fl, PLT 80.000/mmc. LDH 175 UI/L. Monoclonal gammopathy IgM/Kappa 2,7 g/L was detected. ANA and rheumatoid factor tested negative. Ab anti-cardiolipin resulted positive for IgM with negative LAC. Serum IL-6 and IgG4 resulted within the normal range. Abdomen US revealed deep lympho-adenopathy. A CT-PET scan was then performed, resulting in pathological uptake in bilateral iliacs lymph-nodes (SUV 12.5), multiple lymph-nodes in anterior abdominal wall (SUV 8.9), paratracheal lymph-nodes, left axillary lymph-nodes (SUV 7.3, ca 14 mm) and bilateral sovra-clavear lymph-nodes. A mass in the mesenterial area (49x53 mm) was observed with SUV 14.6, showing infiltration of the intestinal wall. A paraumbilical subcutaneous node measuring 16 mm was observed with SUV 4.6. Bone marrow examination was negative for lymphomatous and neoplastic infiltration. An excisional biopsy of the left axillary lymph-node was performed.

Biopsy Fixation Details

48h in 10% Formaldehyde.

Frozen Tissue Available

Yes.

Details of Microscopic Findings

The normal lymph-node architecture is mostly preserved. B lymphoid follicles are characterized by germinal centers showing conserved meshwork of follicular dendritic cells, with few focal signs of colonization. Some features of Castleman disease, such as “onion skin” follicles and penetrating vessels, are occasionally observed. Interfollicular areas are made of mature T-lymphocytes, mature plasma cells, eosinophils and scattered CD30+ activated cells. Immunostainings highlight aggregates of intrafollicular mature plasma-cells, showing IgG4 positivity (>400 x 10 HPF, IgG4/IgG ratio >40%) and Kappa chain restriction. EBV and HHV8 tested negative.

Immunophenotype

N/A

Cytogenetics

N/A

Molecular Studies

Ongoing testing of IGH, Light Chains and TCR clonality.

Proposed Diagnosis

Atypical IgG4+ Lymph-node plasmacytic proliferation vs. Nodal Marginal Zone Lymphoma.

Interesting Feature(s)

This rare case represents a diagnostic challenge in rendering a clear-cut diagnosis of lymphoma with plasmacytic differentiation in the context of intrafollicular IgG4+, Kappa-restricted plasmacytosis. In our case, the patient presents with multiple lymphadenopathies and only mild signs of autoimmunity (IgM+ anti-cardiolipin) of uncertain significance, with no other symptoms and modest serum IgM/K gammopathy; serum IgG4 and IL-6 are not suggestive of systemic Castleman disease or IgG4-Related Disease. The clinical and radiological suspicion of indolent B-cell lymphoma cannot be clearly confirmed on the basis of histological and immunohistochemical studies on lymph-node, showing only focal signs of follicular colonization. Bledsoe JR et al (AJCP, 2017) reported few cases of atypical IgG4+ plasmacytic proliferation, some arising in the context

of autoimmune or inflammatory processes, with no clear diagnosis of lymphoma. These cases represent a clinical and pathological dilemma as they may be the result of chronic immune stimulation or an early clonal event which may develop in an overt lymphoma over time.

EA4HP24-LYWS-318

Hyaline Vascular-type Unicentric Castleman Disease (HV-UCD) with Probable *SRP72* Germline Mutation

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Case Description

A 49F presented in 2018 with enlarged right cervical lymph nodes (LNs). She had past history of right thyroid lobectomy for nodular goiter & left thyroid lobectomy for **follicular carcinoma** with an incidental papillary microcarcinoma. She has been on synthyroid & recently had enlarged **right** cervical LNs. Level 2A, 3 & 4 right cervical LNs were excised & fixed in 10% NBF. The largest Level 4 LN showed histologic changes described under microscopic description. Whole-body PET/CT Scan showed no lymphadenopathy & no other mass lesions. Complete blood count (CBC), clinical chemistry panel (including albumin & globulin levels), CRP, ESR, & ANA testing were normal. HIV Testing was negative. Follow-up whole-body PET/CT Scans, CBCs, clinical chemistry panels, CRPs, & ESRs were normal. She had no other symptoms or signs & got no medical treatment other than synthyroid. She had rectal bleeding about 6 months ago & colonoscopy detected an 8 cm sigmoid colon tubulovillous adenoma (TVA).

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

No

Details of Microscopic Findings

LN shows large lymphoid follicles with mostly regressed germinal centers (GCs) with twinning & budding of GCs. Concentrically-arranged mantle cells & dendritic cells ("Onion-skinning") & focally a straight capillary running into the follicle center ("lollipop") are also noted. Interfollicular areas show increased vascularity.

Immunophenotype

Immunohistochemistry: Most of non-GC lymphocytes: +ve for CD20, BCL2, IgD, & TCL1 with some of mantle zone cells are CD23+ve. GC cells: +ve for CD20/CD10/BCL6/Ki67, & -ve for BCL2. Follicular dendritic cells : +ve for CD21, CD23 & EGFR. A few interfollicular plasma cells: CD138+/MUM1+. Clusters of plasmacytoid dendritic cells : +ve for CD31 & CD68. Increased vascularity: +ve for CD31. CD3+/CD5+ cells & CD30+ cells show rimming of GCs.

Cytogenetics

Not done

Molecular Studies

In Situ Hybridization: Admixture of kappa & lambda mRNA+ve cells; EBER.-ve

TCR Gene Rearrangement Studies: - ve

FISH for BCL1/IGH Translocation: - ve

NGS (DNA & RNA; 249-Gene Panel): a VUS (*SRP72* R324C mutation at 51.5% VAF)

Proposed Diagnosis

Hyaline Vascular-type Unicentric Castleman Disease (HV-UCD) with Probable *SRP72* Germline Mutation

Interesting Feature(s)

1. We have all diagnostic features of HV-UCD.
2. Multiple tumors over time:**Left-sided** follicular carcinoma & papillary microcarcinoma of thyroid, UCD of **right** cervical LN & large TVA of colon.
3. Probable germline *SRP72* mutation: VUS (missense mutation) in *SRP72* at 51.5% VAF
4. An inborn error of immunity (IEI): SRP72 protein deficiency due to *SRP72* germline mutations, which has been related to aplastic anemia (AA), myelodysplastic syndrome (MDS) & congenital nerve deafness [*J Clin Immunol. 2020;40:24-64; Future Rare Dis. (2021)FRD11 10.2217/frd-2020-0003; Am J Hum Genet. 2012;90:888-892]*.
5. *SRP72* mutation at 51.5% VAF (an inborn SRP72 protein deficiency, i.e an IEI): It could be a factor in pathogenesis of follicular carcinoma & a papillary microcarcinoma of thyroid, UCD & a large TVA of colon, but it is not causing AA, MDS or congenital nerve deafness.
6. *None of PDFGRB, FAS, FGFR3, NF1, IL6ST, HRAS, KRAS, NRAS, ERBB4, JAK1, JAK2, JAK3, BRAF, TGFBR2, PIM1*, & *AKT1* mutations seen in UCD (*Leukemia. 2019;33:1035-1038; Biology. 2021;10:251; Front. Oncol. 2022;12:857606*) are seen in our case.
7. SMA/p53 +ve spindle stromal cells harboring *PDGFRB* N666Smutation: These have been seen in UCD *(Front. Oncol. 2022;12:857606. doi:10.3389/fonc.2022. 857606*), but we did not find them.

EA4HP24-LYWS-332

Pediatric in situ lymphoma and castleman disease – possibilty for progression or presence of sinchronous diseases

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Case Description

A child, 7.5 years old with a history of previously diagnosed Pediatric In Situ Folicullar Lymphoma, treated by 'watch and wait' strategy has been admitted at the Pediatric University Clinic, Skopje, in February 2023.

In June 2022, due to worsened generalised lymphadenopathy (No.1206640) and symptoms of anaemia, thrombocytopenia and slight splenomegaly, new lymph node biopsy has been done.. The obtained diagnosis was Atypical Lymphoid Hyperplasia.

In February 2023, the child was again admitted to the hospital with signs of coughing and dyspnea. On physical examination there were found increased cervical lymph nodes and metabolic disease in the mediastinal and abdominal lymph nodes as well as in the spleen and lung parenchyma.

Biopsy Fixation Details

First surgical lymph node biopsy - not available.

Second (No.1206640) and third surgical lymph node biopsy (No. 1218211) measuring 6x4x2cm and half of lymph node (3.5x1.7x1.5cm), respectively, fixed neutral formaline fixed for 36 hours.

Frozen Tissue Available

Is not available.

Details of Microscopic Findings

(No.1218211) Histological analysis showed severe folicullar and paracortical hyperplasia with progressively transformed foliculles and follicular colonisation from the mantle/marginal zone cells. Starry sky feature has been lost in some germinal centers. Focally one could see proliferation of thel epitheloid venules in the paracortical tissue. Mitotic figures were fpresent. Differential diagnosis was done: In situ Follicular Lymphoma, In Situ Marginal Zone Lymphoma, and Castelman disease.

Follow up of the child revealed worsening of the clinical manifestations with severe dyspnea and severe mediastinal lymphadenopathy with focal infiltrative lesions in the lung parenchyma.

Revision of histology with additional immunohistochemical staining for HHV8 was done. Supprisingly, We found positivity in rare endothelial cells and in a few lympohoid cells in

the sections of the second biopsy (No. 1206640) while the sections from the third biopsy (No. 1218211) were negative. Diagnosis of Castleman disease has been established.

Immunophenotype

(No. 1206640 and 1218211): CD20 and PAX5 strong expression in the follicular structures with high proliferation on Ki67. Bcl2 revealed regular perifolicullar strong expression and few cells in rare foliculles in the second biopsy (No. 1206640). CD3, CD4 and CD8 were strongly positive in paracortical lymphoid tissue with increased presence of CD3+/CD4+ cells in the germinal centers. Ki67 showed increased activity up to 15-20% in the paracortical tissue. CD30, CD15 and EMA were negative for HODGKIN`s and Reed Sternberg cells. We found aberrant expression of IgA in some germinal centers and positivity for HHV8 in 3 to 5% of the cells in paracortical region (No. 1206640).

Cytogenetics

Not performed.

Molecular Studies

: Except tests for monoclonality in first biopsy, not performed..

Proposed Diagnosis

CASTELMAN DISEASE, PAEDIATRIC IN SITU FOLLICULAR LYMPHOMA can not be excluded.

Interesting Feature(s)

Diagnosis of Castelman’s disease was established by morphological and immunohistochemical analysis with expression of HHV8 in endothelial cells together with the clinical findings for mediastinal lymphadenopathy and infiltrative lesions in the lung parenchyma. It is questionable if there was pitfall in the analyses done in the first biopsy, where monoclonality for IGH and IGK was found and diagnosis of PEDIATRIC TYPE IN SITU FOLLICULAR LYMPHOMA has been established instead of ATYPICAL LYMPHOID HYPERPLASIA. Otherwise evolution of the disease to CASTELMAN DISEAESE or synchronous existence of both diseases should be observed.

EA4HP24-LYWS-334

B-cell marker silent large B-cell lymphoma HHV-8+ arising in a pacient with multicentric Castleman disease

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Case Description

Male, 45 years-old, with a history of HIV diagnosed in 2020 (well controled with Biktarvy -bictegravir/emtricitabina/tenofovir-) and multicentric Castleman disease associated to HHV-8 diagnosed in 2022. After 4 cycles of rituximab and 6 cycles of R-COP he presented clinical signs of progression, with a PET that highlighted increased uptake of FDG in lymph nodes, muscle and intestine. At that moment, the HHV-8 viral load in blood was of 140.000 copies. A supraspinatus muscle core biopsy was performed.

Biopsy Fixation Details

Formalin-fixed and paraffin-embedded tissue

Frozen Tissue Available

No

Details of Microscopic Findings

Fibroadipose tissue core biopsy infiltrated by a diffuse proliferation of large cells with centroblastic, immunoblastic and plasmablastic morphology. The neoplastic cells were arranged in sheets and between collagen fibers. In some areas, a starry sky pattern was observed, with numerous apoptotic bodies and atypical mitotic figures.

Immunophenotype

The neoplastic cells were diffusely positive for MUM1, CD30, and HHV-8, and focally positive for OCT2. CD138 was very weak in isolated cells. CD20, CD79a, CD19, PAX5, IgM and Bcl2 were negative. The proliferative index assessed with ki67 was 90%. EBER and ALK were negative. CD2, CD3, CD5 and CD7 highlighted the abundant reactive T-cell infiltrate. CD7, however, was also positive in tumor cells. Light chains immunostains showed occasional polytypic plasma cells, but were negative in the neoplastic cells.

Cytogenetics

FISH for *MYC* with break-apart probes did not show any rearrangement or copy number alteration for this gene.

Molecular Studies

B and T-cell clonality studies showed a clonal IGH rearrangement (regions FR3 and FR1), and a polyclonal pattern of the beta and gamma chains of the TCR. NGS with a custom panel that includes 60 genes commonly mutated in B and T-cell lymphomas revealed a

likely pathogenic frameshift mutation in *FAS* (p.Thr241HisfsTer7; allele frequency: 15,25%), a pathogenic missense mutation in *HRAS* (p.Gly13Arg; allele frequency: 4,20%), and a variant of unknown significance in *STAT5B* (p.Asp575Asn; allele frequency: 14,25%).

Proposed Diagnosis

Large B-cell lymphoma, CD30-positive, associated with HHV-8

Interesting Feature(s)

Classification of this case is difficult. It is a large cell neoplasm, CD30-positive, without clear expression of B or T-cell markers, associated with HHV8 in the absence of EBV. Negativity for immunoglobulins and B-cell markers does not support the diagnosis of DLBCL associated with HHV-8, while negativity for CD138 and EBV goes against the diagnosis of a solid variant of a primary effusion lymphoma (although some EBV-negative cases have been described). The expression of CD7 by the neoplastic cells also introduces the T-cell lymphoma associated with HHV8 in the differential diagnosis, although this is ruled out with the clonality studies showing a clonal IGH rearrangement and a polyclonal TCR.

EA4HP24-LYWS-341

Follicular dendritic cell sarcoma arising in a background of Castleman disease

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Case Description

70year old female, without relevant medical history, presents in november 2020 epigastric pain.

CT abdomen shows a tumoral mass hepatogastric ligament, radiologically differential diagnosis was GIST? Carcinoid? Fibrous tumor? Other?

PET shows a strongly hypermetabolic mass hepatogastric ligament

Patient underwent a partial gastrectomy and lymphadenectomy.

Upon macroscopical examination a large nodule (6,5x3x2,5cm) was found in the subserosal fat, with a firm, pale nodular aspect.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

no

Details of Microscopic Findings

Cross sections of corpus-type gastric wall. The serosa contains a rather sharply delineated lesion in which numerous anastomosing lymphoid follicles can be distinguished. However, the follicles often contain no or only a small atretic germinative centers, while the surrounding mantle zone shows concentric expansion. Some of these follicles contain

centrally prominent blood vessels with hyaline walls. Dilatation of the intervening sinusoids is present, which are filled with numerous epithelioid histiocytes. The paracortical zone between these follicles is dilated. Locally, a multifocal and remarkably clustered proliferation of large and plump fusiform to epithelioid cells is seen, occasionally in a limited storiform configuration (to form "whirls"). These contain a moderately ample amount of pale amphophilic cytoplasm and a remarkably large, vesicular nucleus with one or more prominent nucleoli. Some of these cells even contain 2 nuclei, and rare multi-core 'Warthin-Finkeldey' cells can also be found. The anastomosing cell clusters are partially separated by broad fibrous septa with hyaline aspect. Overall, few mitotic figures are found, but in a single location, 5 mitotic figures per 10 high power fields are easily found, however, never more than 10 per 10 high power fields. We see no overte cytonuclear atypia and no necrosis.

Immunophenotype

B-cell nodules (mature naive B), supported by FDC networks

- Positive for: CD20, PAX5, IgM, IgD, CD23 weak
- Negative for: LEF1, CyclinD1, CD5, SOX11
- Low number of plasma cells, but predominantly lambda

Focal FDC proliferations:

- Positive for: CD21, CD23, CD35
- Negative for: CD117, ALK, EMA, HHV8, CD30, ERG, CD15, EBER, CD1A, S100
- Low proliferation Ki67

Cytogenetics

n/a

Molecular Studies

PCR: Polyclonal result for BCR

mutation analysis ongoing

Proposed Diagnosis

Follicular dendritic cell sarcoma (low grade) arising in a background of unicentric Castleman disease

Interesting Feature(s)

•Follicular dendritic cell sarcoma (low grade) arising in a background of unicentric Castleman disease

•Patient is in complete remission after 3 years

EA4HP24-LYWS-342

HHV8-Related Multicentric Castleman's disease with EBV coinfection and reactivation

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Case Description

A 50-year-old male Caucasian patient presented with asthenia, fever and weight loss since two months. Physical examination disclosed splenomegaly and multiple lymphadenopathy. Serum HIV testing gave negative results, whereas testing for EBV-DNA and HHV8-DNA was positive. Other causes of immune disregulation were excluded. Incisional biopsy from an external iliac lymph node was performed and the sample was sent to the pathology department for the diagnostic workup.

Biopsy Fixation Details

Fixation was performed in neutral 10% buffered formalin for 24 hours, the tissue was cut into 2-mm-thick section and paraffin-embedded.

Frozen Tissue Available

No frozen tissue was taken.

Details of Microscopic Findings

Histological examination of the lymph node showed a preserved architecture characterized by follicular hyperplasia with atrophic-hyalinized germinal centers surrounded by onion skin-like mantle zones and occasionally with radially penetrating blood vessels . Follicular dendritic cell meshwork (CD21+; CD23+) was reinforced with dysplastic changes. There were increased mature plasma cells in the interfollicular areas which were polytypic for κ and λ immunoglobulin light chains and exhibited a normal IgG/IgG4 ratio. HHV8 positivity was demonstrated by LANA immunostain in scattered plasmablasts in mantle zones and in germinal centers which showed IgM positivity and λ light chain restriction. Interestingly, EBV presence was demonstrated in blasts with almost complete colonization of some germinal centers (EBER-ISH+) as well as in focally scattered cells in the interfollicular areas. Immunostaining for ZEBRA highlighted scattered positive cells indicating reactivation of the lytic cycle of EBV.

Immunophenotype

Immunohistochemistry for CD20, CD79a, PAX5, CD3, CD21, CD23, MUM-1/IRF4, HHV8 (LANA-1), and EBV encoded ribonu-cleic acids by in situ hybridization (EBER-ISH), ZEBRA, CD38, CD138, κ light chain, λ light chain, IgM, IgG, IgG4 and CD30 was performed.

Cytogenetics

No cytogenetic study was performed.

Molecular Studies

No molecular study was performed.

Proposed Diagnosis

KSHV/HHV8 multicentric Castleman's disease associated with infection and reactivation of EBV.

Interesting Feature(s)

Our case raise the question of the pathogenetic role of a synchronous infection by HHV8 and EBV. EBV reactivation and expression of *BZLF1* may influence clonal evolution in HHV8-related LPDs (Münz C. 2019, Granai et al. 2021). In fact, the co-infection of these two oncoviruses may prompt for a more rigorous follow-up of the patient in order to rule out a possible progression to a HHV8+/EBV+ lymphoproliferative disorder. Our patient responded well to rituximab therapy and remains with no symptoms after 8 months of follow-up.

Münz C. Latency and lytic replication in Epstein-Barr virus-associated oncogenesis. Nat Rev Microbiol. 2019 Nov;17(11):691-700. doi: 10.1038/s41579-019-0249-7. Epub 2019 Sep 2. PMID: 31477887..

Granai, Massimo, et al. "Epstein–Barr virus reactivation influences clonal evolution in human herpesvirus-8-related lymphoproliferative disorders." Histopathology 79.6 (2021): 1099-1107.

EA4HP24-LYWS-362

Unicentric Castleman Disease with Hyaline Vascular Morphology and Lambda Light Chain Predominance

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Case Description

A 39-year-old otherwise healthy female presents with persistent abdominal discomfort and pressure symptoms, more pronounced after heavy meals. A CT- scan of the abdomen revealed a large left mesenteric mass ~7 cm in the largest dimension with left periaortic lymphadenopathy. Fine needle aspiration and needle core biopsy of the mass were considered reactive with polyclonal B-cells and T-cells. Over the next eight years the mass increased to ~10 cm with some calcifications. No other adenopathy or organomegaly was noted. The patient underwent surgical resection of the mass.

On follow up, serum protein electrophoresis showed no monoclonal proteins. Post-surgical PET/CT scan (skull base to mid-thigh) showed no adenopathy, organomegaly, or hypermetabolic lesions. The patient has been essentially asymptomatic after surgery for six months.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections from the mass showed overall preserved lymph node architecture. The follicles were frequently large, with expanded mantle zones and atrophic germinal centers. Occasional follicles showed multiple germinal centers. The background shows extensive fibrosis/sclerotic changes and prominent hyaline vascular changes. Foci of calcification were appreciated. Occasional vessels were noted penetrating the follicles, creating the classic “lollipop sign”. No atypical large cells, areas of necrosis, or granulomas were identified. Perisinusoidal and perivascular areas show plasmacytosis. Some areas showed relatively prominent sinus histiocytosis.

Immunophenotype

PAX5/ CD20 highlights B-cells in predominantly follicular areas. The B-cells are negative for CD5 and CD43. KI67 highlights expectedly high proliferation within the scant germinal center areas and otherwise a very low proliferation index. Cyclin D1 is negative in lymphocytes. HHV8 and cytokeratin cocktail were negative. S100 showed no significant staining. EBV-LMP1 and EBER (by in situ hybridization) are negative. CD138 and MUM1 highlight mild plasmacytosis. Kappa and lambda interestingly highlight lambda light chain predominance in plasma cells. IgG highlights the majority of plasma cells and has infrequent IG4 expression. All stains had adequate controls.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Castleman Disease, hyaline vascular variant, HHV8 negative

Interesting Feature(s)

The case presents a typical manifestation of unicentric hyaline vascular Castleman disease with longstanding pressure-related symptoms and no cytokine-mediated manifestations. Excisional biopsy was both diagnostic and curative.

Perivascular/ Perisinusoidal plasmacytosis with lambda light predominance is of unclear significance. The plasma cell population caused no tissue effacement with a rather overall reactive distribution pattern. The patient had no monoclonal gammopathy on follow-up testing. The patient is asymptomatic, especially with normal range peripheral blood counts and absence of kidney issues, adenopathy/ organomegaly, skin lesions, endocrine symptoms, or neuropathy.

EA4HP24-LYWS-369

Unicentric Castleman Disease with Atypical Stromal Spindle Cell Proliferation and Indolent T-lymphoblasts in an HIV patient

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Case Description

We present a case of a 56-year-old man with a history of alcohol and cannabis use, former intravenous drug use (IVDU) for over 20 years, and HIV-positive status on bictegravir-based antiretroviral therapy (ART) with a current undetectable viral load. He also has hepatitis C virus (HCV)-related hepatopathy with bile duct dilation due to choledocholithiasis and is undergoing treatment with sofosbuvir/velpatasvir. Past medical history includes cholecystectomy in 2014 and attempted endoscopic retrograde cholangiopancreatography (ERCP). In 2021, he was hospitalized due to obstructive jaundice secondary to choledocholithiasis. A CT scan revealed a right renal pelvis mass with hypervascular features, cystic degeneration, irregular borders, but without clear infiltration into nearby structures, enlarged inguinal lymph nodes (20 mm), and mild liver and spleen enlargement. The patient underwent pelvic mass excision and hepaticojejunostomy.

Biopsy Fixation Details

FFPP (formalin-fixed, paraffin-embedded)

Frozen Tissue Available

No

Details of Microscopic Findings

- Hyaline vascular features: extensive proliferation of high endothelial venules with perivascular hyalinization, twinning of mantle zones, atretic germinal centers and follicular dendritic cell expansion with discrete atypia
- Prominent interfollicular stromal spindle cell proliferation with no obvious follicle effacement
- Focal moderate-to-marked dysplastic features in stromal spindle cell proliferation
- Multifocal perifollicular dense TdT+ T-lymphoblast proliferation associated with stromal spindle cells

Immunophenotype

- Interfollicular stromal spindle cells: SMA (+), CD68 (+/-), CD31 (-/+), EMA (-/+). Negative for CKAE1-AE3, S100, Desmin, CD21, CXCL13, CD23, D2-40; mild increase in p53 expression in dysplastic cells
- Follicular dendritic cells: (+) CD21, CXCL13, CD23; positivity limited to follicles
- Lymphoblasts: (+) TdT, CD3, CD4, CD8, CD99, CD1a, CD10 (+/-), CD5 (+/-), CD7 (+/-). Negative for CD34
- EBER ISH positivity in sparse paracortical cells (HIV context)

Cytogenetics

No

Molecular Studies

- No mutations found in PDGFRA exons 12 and 18
- PDGFRB mutation status not assessed
- IGH (FR1, FR2 and FR3), IGK (Kde), TCR-β and -γ clonality studies were polyclonal

Proposed Diagnosis

Unicentric Castleman Disease (hyaline vascular variant) with atypical stromal spindle cell proliferation

Interesting Feature(s)

- Unicentric Castleman disease (UCD) in HIV patients is rare, while multicentric variant is more frequent. Our case exhibits unicentric presentation with hyaline-vascular pattern and extranodal involvement.
- Dendritic cell expansion has been widely reported, commonly of the follicular dendritic type. Dendritic cells may show varying degrees of dysplasia, some displaying discrete increased expression of p53. Reticular type and "angiomyoid" dendritic proliferations – as in our case – are challenging to classify among subtypes.
- T lymphoblast proliferations have been described in UCD, often associated with dendritic proliferation. It is crucial to emphasize the reactive/indolent nature of lymphoblasts to distinguish from T-cell lymphoma.
- Castleman's disease is recognized as a polyclonal LPD with significant upregulated and downregulated genes. A subset of UCD may exhibit clonal cytogenetic and molecular alterations, such as mutations in PDGFRB. This raises the question on where histological and molecular criteria lie to differentiate such dendritic proliferations from low-grade sarcoma. These mutational studies were not performed in our case.

EA4HP24-LYWS-381

Multicentric Castleman Disease

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Case Description

48 year-old female , HIV positive, untreated diffuse lymphadenopathy and splenomegaly. ? lymphoma, ? TB ? other. No clinical features suggestive of an autoimmune disorder. Histochemical stains for microorganisms were negative.

Biopsy Fixation Details

Formalin-fixed tissue

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph node with distorted architecture including an intact capsule and open sinuses. A vaguely nodular pattern and expanded interfollicular area. Many nodules have follicles and the nodules contain large cells with blastic morphology (reminiscent of immunoblasts and plasmablasts). These large cells have open chromatin and prominent nucleoli. Most germinal centres are not associated with clearly defined mantle zones and some contain prominent penetrating venules and small aggregates of plasmablasts. However, many germinal centres are completely effaced by plasmablasts. There is no diffuse sheetlike arrangement of large lymphoid cells.

Immunophenotype

Most vaguely-defined nodules have CD21 and CD23 positive FDC networks. The cells within these nodules reflect a reduced number of small-medium cells, that are usually present at the rim and these are mostly CD20+ cells. The large blastic cells in the nodules are positive for Mum-1, IgM, HHV-8; weakly positive for lambda light chain; partly positive for CD30 and c-myc; and negative for CD138, CD19, CD5, CD23, cyclinD1, CD56, CD117 and Alk-1. The proliferative fraction by Ki67 labeling is approximately 45%.

In the interfollicular / internodular areas there is a reduced numbers of small -medium sized lymphoid cells, which are mostly CD3 and CD5 positive T-cells that express Bcl-2. The sheets of mature appearing plasma cells are positive for CD138 and IgG, and demonstrate slight kappa predominance but no clearly defined light chain restriction. Further, these are negative for CD117, CD20 and cyclinD1.

Throughout the biopsy there are scattered EBER positive cells, scattered CD10 and Bcl-6 positive cells, and occasional interspersed large cells positive for CD30. CD34 highlights the blood vessels including those penetrating in the germinal centres

Cytogenetics

None

Molecular Studies

Polyclonal Ig heavy chain gene rearrangements and a small clonal peak (198bp) in the Ig light chain gene rearrangements using V-J primer set.

Proposed Diagnosis

Multicentric Castleman disease, HHV8+, in a setting of HIV infection

Interesting Feature(s)

Prominence or onion-skinning of mantle zones not present. There is differential expression of immunoglobulin light chains; lambda light chains in plasmablasts in the nodules and slight kappa light chain excess in normal appearing plasma cells in the interfollicular areas. A small clonal peak detected in the light chain gene rearrangements. The differential diagnosis includes HHV8 positive germinotropic lymphoproliferative disorder (GLPD). However, GLPD usually (although it has been described in an HIV positive setting and without EBV positivity) occurs in HIV negative patients and the plasmablasts are usually EBV positive. Further, GLPD is usually a localized disease and in the current there is evidence of generalized disease (diffuse adenopathy and splenomegaly)

EA4HP24-LYWS-385

Incidental, Clinically Silent Early Kaposi Sarcoma Involving an Isolated Lymph Node in an Immunocompetent Patient

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Case Description

The patient is a 69-year-old Caucasian woman with a past medical history of thyroid cancer (2008), retroperitoneal leiomyoma (2012) and renal clear cell carcinoma (2013), who presented in 2016 for removal of a superficial spreading melanoma on the anterior left shoulder. A wide local excision with axillary sentinel node biopsy was performed. The patient had no history of immunotherapy, chemotherapy or other immunosuppressive medication at the time of surgery. In subsequent years, the patient developed breast cancer, treated with excision and sentinel node biopsies and additional melanocytic tumors for which she underwent several resections. No other vascular neoplasms or systemic symptoms developed during seven years follow up in the absence of specific treatment for the nodal lesion.

Biopsy Fixation Details

Non-sentinel lymph node, 10% neutral buffered formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Four lymph nodes were grossly and microscopically unremarkable. One non-sentinel node showed a single, 4-mm focus of a relatively well circumscribed spindle cell proliferation expanding interfollicular and paracortical areas. The spindle cells showed mild pleomorphism, occasional prominent nucleoli and rare mitotic figures. Admixed extravasated red blood cells and rare hyaline globules were seen but no definite vasoformation was present.

Germinal centers were increased in number, many atretic, and admixed within the spindle cell proliferation. Some showed Castleman-like features: mantle zone cells concentric layering and hyperplastic hyalinized vessels. These findings were not seen away from the lesion or in other lymph nodes. Plasma cells were not increased and plasmablasts were not seen. All nodes were negative for metastatic melanoma.

Immunophenotype

The spindle cells expressed CD31, ERG, D240, vimentin, and HHV8; and were negative for CD21, CD23, EBER, S100 and all hematolymphoid markers. B and T cells showed unremarkable distribution and phenotype. Plasma cells were polytypic and negative for HHV8. HHV8 was negative in all other lymph nodes tested. Periodic Acid-Schiff highlighted hyalinized vasculature.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

Incidental early Kaposi sarcoma involving lymph node with associated Castleman-like changes

Interesting Feature(s)

Kaposi sarcoma (KS) is usually multifocal in AIDS patients involving primarily the skin and mucosae. Nodal involvement is mostly seen in extensive disease and only extremely rarely in isolation.

Incidental KS is rare in immunocompetent patients without mucocutaneous involvement, but always identified clinically or radiologically and followed by disease progression.

HHV8 is positive in plasma cells in multicentric Castleman disease (MCD). Plasma cells as well as dendritic cells in the CD-like follicles were HHV8 negative in this case. No other KS lesions or MCD symptoms were present at the time of surgery or have developed over seven years follow-up.

Rare cases of lymphadenopathy with KS and MCD-like features exist,but this is the first report of a solitary, microscopically detected, clinically silent and non-progressive early nodal classic KS to our knowledge. Early localized HHV8 reactivation and related tumorigenesis could remain undetected and may not harbinger systemic disease or progression, therefore treatment may not be warranted.1. Abe Y, et al. Pathol Int. 2006. PMID: 16984619.

2. Xerri L, et al. Arch Pathol Lab Med. 1991. PMID: 1747036.

3. Courville EL, et al. Am J Clin Pathol. 2014. PMID: 25389336.

4. Kennedy MM, et al. Mol Pathol. 1998. PMID: 9624414

EA4HP24-LYWS-390

Spectrum of IgG4 related disease in node : Castleman like Follicular hyperplasia followed byclonal germinal center proliferation

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Case Description

A 59 male presented in June 2018 with multiple swellings in the B/L neck gradually increasing in size with B symptoms.

PET scan revealed Right level II node, measures 18x9 mm, SUVmax: 5.09 Left axillary and retropectoral nodes, largest measures 29x19 mm, SUVmax: 12.00.

Cervical node biopsy was done and called reactive hyperplasia.

Patient was observed but he continued to have B symptoms and weight loss. On follow up his CRP was 96 mg/dl but ANA, DsDNA were negative. Serum IL6 was normal. Was thought to be multicentric Castleman's disease and put on a course of hydroquinone's and prednisolone with relief of symptoms and regression in all nodes except the axillary node. Patient followed up till 18/1/2020 at which point his symptoms returned and CECT showed multiple enlarged nodes.. Repeat axillary node biopsy was done and this is second sample provided.

Post second biopsy patient was oberved again . In Dec 2020 was diagnosed autoimmune pancreatitis and found to have raised serum IgG4 levels (detailed report not available) at another hospital. His globulins even at presentation were 6.7g/DL and there was polyclonal hypergammaglobulinenia. He had no renal manifestations. His IgE levels were raised.

Patient was given a course of steroids with marked improvement. in 2021 patients adenopathy progressed further and received two doses of single agent rituximab(500mg) with no nodes further palpable. Patient contacted on 14th Jan 2024 and was asymptomatic.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sample 1

•Node showed follicular hyperplasia with reactive follicles , some of these showed denritic cells with whorling and perforating vasculature mimicking castlemans disease.

Sample - 2 This node showed a large nodule with progressive transformation of germinal center like area in center occupying about two thirds of node. The nodules essential was conglomerate of germinal center and expanded mantle zones.

Immunophenotype

Sample 1

On immunohistochemistry this node showed CD20 positive germinal centers and paracortexshowed T cells which were CD4/CD7 and CD3 positive.The only thing atypical about the proliferation was that germinal centres showed low Ki67 . Please note increased IgG4 positive cells were found in nodes with IgG4: IgG ratio of 30%. This immunostain was done at later date in 2020.

Sample 2

The nodule was composed of expanded conglomerate of follicles (CD10, bcl6 positive) that were bcl2 negative but surrounded by IgD positive mantle zone. CD23 revealed patchy retained dendritic network in that area.

In the T zone CD3 positive cells were CD5 and CD4 positive, CD8 remained scattered.

IgG4: IgG was same as above biopsy which was done after the clinical diagnosis. The MIB1 of follicles was very high as opposed to previous biopsy. Diagnosis of atypical follicular hyperplasia was given.

Cytogenetics

No

Molecular Studies

The nodule was cored out and Clonality was done on that. There were clonal peaks observed in IgH tube A and C while TCR was polyclonal.

Proposed Diagnosis

Nodal involvement in IgG4 related disease with Castleman's like hyperplasia progressing to a clonal germinal center proliferation

Interesting Feature(s)

The histopathological features of IgG4 encountered in present case were unusual - The plasma cells were not very evident , there was no fibrosis or eosinophil.The disease mimicked Castleman's disease closely in first biopsy and showed progression to a clonal germinal centre proliferation. We have not come across any such similar case in literature.

EA4HP24-LYWS-393

TAFRO/POEMS syndrome in a young patient with multicentric Castleman disease

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Case Description

A 20 year old male with no past medical history presented to our institute with increasing abdominal distension, lymphadenopathy, fevers, anasarca, splenomegaly, hypothyroid, microcytic anemia, and renal dysfunction. The patient has had several bone marrow biopsies at an outside institute that were unrevealing.

A lymph node biopsy was performed. Imaging showed adenopathy including a left supraclavicular node measuring up to 1.2 cm and bilateral axillary adenopathy, as well as borderline enlarged mediastinal lymph nodes.

A lymph node biopsy showed morphologic features of Castleman disease with no evidence of malignacy. He also had an elevated IL-6, VEGF and kappa light chains. He had to have paracentesis on several occasions and eventually was initiated on siltuximab and discharge with ascites.

A bone marrow biopsy showed hypercellular marrow (>95%) with trilineage hematopoiesis and megakaryocyte hyperplasia. There was moderate diffuse reticulin fibrosis (MF 2 of 3) and normal iron storage.

On follow up, 6 weeks later, the patient has stopped pain medication, has not had fever, night sweats and had lost almost 50 pounds of fluid. His hemoglobin improved from 6.5-14.2 x 10^9/L. His kappa light chain levels and CRP are now normal.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The lymph node is enlarged and shows slightly distorted architecture with paracortical expansion. There are frequent reactive lymphoid follicles, which contain frequent atretic germinal centers with proliferation of capillaries and follicular dendritic cells in the germinal centers. Vessels penetrating into the germinal centers and twinning of germinal centers sharing follicles are identified. The mantles are expanded. The interfollicular areas are expanded and consist of small reactive lymphocytes with no overt cytologic atypia, increased fibrous deposition, and increased vasculature.

Abundant interfollicular plasma cells are identified. No large atypical lymphocytes, Hodgkin Reed-Sternberg (HRS) cells, or metastatic tumor are identified. The sinuses are patent and filled with histiocytes and small lymphocytes.

Immunophenotype
HHV8: Negative
EBER-ISH: Negative
Kappa /lambda-ISH: Polytypic population of kappa and lambda plasma cells, ratio ~2:1
Cytogenetics
46,XY[16] Normal Male
Molecular Studies
None
Proposed Diagnosis
HHV8 negative multicentric Castleman disease with borderline case of TAFRO/POEMS
Interesting Feature(s)
The course of TAFRO syndrome is acute, with rapid deterioration and serious disease unlike in isolated Castleman disease. Early recognition can prompt timely treatment.

EA4HP24-LYWS-397

Expanding the spectrum of KSHV/HHV8 disorder: Multicentric Castleman Disease associated with increase of IgG4 positive plasmacells.

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Case Description
An 81-year-old female with no significant medical history was admitted for bowel obstruction. An excisional biopsy was performed on a 2.7 cm superior mesenteric artery lymph node.
Biopsy Fixation Details
The lymph node was fixed in 10% buffered formalin.
Frozen Tissue Available
No.
Details of Microscopic Findings
Lymph node biopsy showed an architecture preserved with the presence of many hyperplastic germinal centers. However, few regressed sclerohyaline germinal centers, characterized by penetrating vessels with concentric “onion-skin” mantle zones, were also observed. The presence of HHV8 virus was investigated by using the latency-associated nuclear antigen (LANA) immunohistochemical stain, which was focally positive in scattered plasmablasts both in the interfollicular areas and in the germinal centers. Moreover, sheets of policlonal plasmacells were present in the interfollicular areas with an icreased

accumulation of IgG4+ plasmacells within the germinal centre (IgG4 >100/HPF; IgG4/IgG ratio >40%); however, the other histological features of IgG4 related disease, such as storiform-type fibrosis and obliterative phlebitis, were absent.

Immunophenotype

CD20, CD38, CD138, CD21, CD23, CD30, IgG, IgM, IgD, IgG4, Kappa and Lambda light chain, EBER-ISH, HHV8 LANA.

Cytogenetics

46, XX

Molecular Studies

Not performed.

Proposed Diagnosis

KSHV/HHV8-associated related lymphoid hyperplasia with increase of IgG4-positive plasma cells.

Interesting Feature(s)

This case raise the question of differential diagnosis and overlap between KSHV/HHV8-associated Multicentric Castleman Disease (MCD) and immune disregulation with HHV8 related reactive lymphoid hyperplasia. The increase IgG4 plasmacells in the tissue may possibly represent an underlining immune disregulation which may favor HHV8 infection and related reactive lymphoid hyperplasia The exact location for KSHV/HHV8-associated MCD on the spectrum from autoimmune, malignant and infectious diseases is still not well defined and may vary from patient to patient. KSHV/HHV8 associated MCD is a systemic inflammatory disorder driven by IL-6, which is responsible for systemic inflammation and B cell activation; in classic MCD, IL-6 overproduction is driven by HHV8 infection of plasmablasts.In the present case the absence of clinical symptoms may favor the diagnosis of KSHV/HHV8-associated related lymphoid hyperplasia. IL-6 expression in an important factor in MCD and its expression is related to the symptoms; its serum evaluation as well as its expression by IHC or RNA in situ hybridization may be useful for the accurate diagnosis considering that MCD and IgG4-RD can present in a very similar way, both clinically and histologically; however, the role of IL-6 in IgG4-RD remains unknown, and further studies are needed.

EA4HP24-LYWS-402

Idiopathic multicentric Castleman disease (plasma cell type) with numerous IgG4 positive cells.

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Case Description

In 2017, a Polynesian patient presented with disseminated lymphadenopathy and cystic pulmonary lesions associated with inflammatory syndrome and polyclonal hypergammaglobulinemia. He was unsuccessfully treated with antituberculous therapy. In 2019, a lymph node was removed, which showed an important interfollicular polytypic plasmacytosis with numerous IgG4 positive cells (IgG4/IgG = 40%). As the serum IgG4 level was high (11,4 g/L; N<1,35 g/L), the diagnosis of IgG4 related disease was retained. However, steroid and rituximab therapy weres only partially effective on lymph node and pulmonary lesions. In 2020, a CT guided pulmonary biopsy showed fibrous changes with a polytypic plasmacytosis. In 2022, another lymph node was surgically removed and the same pathological features as in 2019 was observed. Due to clinical and histopathological features, the diagnosis of idiopathic multicentric Castleman disease (plasma cell type) was retained and the patient was successfully treated with anti-IL6R MoAb therapy.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

available

Details of Microscopic Findings

The architecture of this lymph node is preserved. Some follicles are small with atrophic germinal centers surrounded by a thin mantle zone without typical onion skin aspect. The interfollicular zones are enlarged and are infiltrated by large sheets of small plasma cells with only few lymphocytes. The vascularity is moderately increased.

Immunophenotype

The follicles are CD20+ with reactive germinal center (BCL2 - and CD10 +). In the interfollicular zones, plasma cells stain positive for CD138 and are polytypic on immunoglobulin light chain immunostainings. There are more than 100 positive IgG4 cells/400 field and the IgG4/IgG percentage is around 40%. The LANA immunostaining and the EBER in situ hybridization are negative.

Cytogenetics

none

Molecular Studies

none

Proposed Diagnosis

Idiopathic multicentric Castleman disease (plasma cell type) with numerous IgG4 positive cells.

Interesting Feature(s)

We describe a case of idiopathic multicentric Castleman disease (plasma cell type) with many IgG4 positive cells. This case illustrates how it is, sometimes, difficult to differentiate IgG4 related disease and multicentric idiopathic plasma cell type Castleman disease.

EA4HP24-LYWS-426

Castleman disease of hyaline-vascular type with extensive ossification

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Case Description

- Male, 46 years old, with previous history of appendicectomy and traumatic back injury.
- Former tobacco smoker.
- No history of hematologic malignancies.
- June 2020: Hospitalized due to unclear high fever, night sweats, malaise and increasing back pain. CT scan showed a 5 x 4.5 x 4 cm well-defined, heavily calcified retroperitoneal tumor ("soft tissue" tumor) localized medial of the left kidney. CT-guided fine needle aspiration (FNA) cytology and needle core biopsy were not diagnostic.
- August 2020: US-CT image fusion-guided needle core biopsy was not diagnostic.
- September 2020: Recurrent fever and increased erythrocyte sedimentation rate (ESR).
- October 2020: Surgical excision of the retroperitoneal tumor (submitted tissue biopsy).

Biopsy Fixation Details

The surgical specimen was fixed in neutral buffered formaldehyde 4% for 48 hours.

Frozen Tissue Available

Not applicable.

Details of Microscopic Findings

The retroperitoneal tumor is composed by lymphoid hyperplastic tissue with vascular proliferation, marked fibrosis and ossification (bone formation). The lymphoid tissue shows numerous lymphoid follicles with regressed germinal centers, many of which are hardly visible, with hyalinization of the vessel walls. A few, scattered, mature plasma cells are seen throughout the lymphoid tissue.

Immunophenotype

Immunohistochemistry showed that the lymphocytic population represent a mixed population of CD20+/CD79a+ B-cells (lymphoid follicles) and CD3+/CD5+ T-cells

(interfollicular areas). The B-cell population is positive for BCL2, partially positive for CD23 and negative for CD5, CD10, BCL6, CD138, Cyclin D1 and p53. The CD138+ plasma cells are polyclonal for Kappa and Lambda light chain expression. The follicular dendritic cell (FDC) marker CD21 reveals the "onion skin" morphology of certain germinal centers.

Cytogenetics

Not applicable.

Molecular Studies

PCR was negative for clonal rearrangements of the IgH and light chain genes.

Proposed Diagnosis

Retroperitoneal Castleman disease of hyaline-vascular type with extensive ossification (bone formation).

Interesting Feature(s)

• Presentation with radiological findings suggestive of soft tissue tumor.

• Extensive ossification (bone formation).

EA4HP24-LYWS-434

ThymicCastlemanDisease&IgG4 RelatedDisease

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Case Description

A 32-year-old female patient, who had been followed up for 12 years with the diagnosis of rheumatoid arthritis and graves disease, underwent contrast-enhanced tomography for pleural effusion. Chest computed tomography revealed a anterior mediastinal lesion, 45x19 mm in size, and lymph nodes, the largest of which was 15x10 mm near the lesion. In PET-CT scan hypermetabolic activity has been detected in this lesion (SUVmax:4.21). serum IgA and IgM were slightly above the limit and serum CRP was constantly high. RF was positive. The patient underwent a biopsy with the preliminary diagnosis of a primary mediastinal mass, such as thymoma. At first evaluation, the patient was diagnosed with Castlemann's disease, and all biopsies and excision material of the lesion were consulted to our department.

Biopsy Fixation Details

formalin 10%

Frozen Tissue Available

no

Details of Microscopic Findings

In hematoxylin-eosin sections, numerous lymphoid follicles and hassal corpuscles were seen in the thymus tissue. Plasma cells were in perifollicular clusters, increased perisinosoidal or concentrated in dense connective tissue areas. The adjacent lymph nodes showed a fibrotic thick capsule, hyperplastic and regressed lymphoid follicles, and

paracortical increased plasma cells. Castlemanoid changes as burn out follicules with enriched follicular dendritic network, “lollipop” appearence of hyalinized vascular germinal centers, “onion skin” like change in mantle zone were observed in some lymphoid follicles.

Immunophenotype

The CD38 stain revealed perifollicular clusters of plasma cells which were stained politypic for kappa and lambda light chains. Most of the plasma cells were IgG positive, and the IgG4/IgG ratio was calculated as 90%. B cells in the follicles were CD20-positive. CD3 was detected in small T cells located in interfollicular areas. HHV-8 was negative.

Cytogenetics

no

Molecular Studies

no

Proposed Diagnosis

Probable IgG4 related disease with castleman disease like features presented with mediastinal Thymic hyperplasia role out Castleman disease

Interesting Feature(s)

Idiopathic Multicentric Castleman disease(iMCD) and IgG4 related disease(IgG4-RD) have some clinical and morphologic overlap, but the differential diagnosis is important for treatment options. Both entity requires spesific exclusions in their essential diagnostic criteria. Even though the patient was followed up due to Rheumatoid arthritis, there were similar changes in the lymph nodes and thymus and interfollicular storiform fibrosis was dominant.

In our case, serum IgA and IgM were slightly above the limit and serum CRP was constantly high. RF was positive. WHO 5th Ed reported that; It is expected that serum IgG4, level is high, LDH, IgM, IgA and CRP levels are normal in IgG4-RD. Serum IgG4 levels are related with disease activity, therefore some caes may have low IgG4 levels. RF may be positive in some cases. But high CRP, IgA and IgM levels are correlated with iMCD in differential diagnosis in the literatüre.

In this case, IgG4-RD as a final diagnosis with Castleman Disease like fetures may be a probable result because; IgG4/IgG ratio >90% , storiform fibrosis, IgG4(+)plasma cells in fibrotic zone of the lymph node. But ruling out Castleman disease is still necessary especially for laboratory findings

EA4HP24-LYWS-439

Idiopathic multicentric Castleman disease.

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Case Description

A 46-year-old man presented with multiple joint pain (knee, fists, ankle) during a two year period, accompanied by weight loss and weakness. There was no history of fever. Laboratory studies demonstrated anemia of chronic disease (Hemoglobin 113, RBC 3.93, MCV 79.8, Fe 5, feritin 372, unremarkable vitamin B12 and folic acid), thrombocytosis (578), increased CRP (23.4) and polyclonal hypergammaglobulinemia (IgG 18.82 g/L). Interleukin 6 level was elevated, measuring 30.3 pg/ml. Imaging studies revealed axillary, inguinal and parailliacal lymphadenopathy. Immunology workup showed no elements of systemic/inflammatory disease. IgG4 levels in the serum were not elevated. Bone marrow biopsy was unremarkable. Core biopsy of enlarged right side axillary lymph node was performed. After the diagnosis was established, the patient was treated with Tocilizumab, and achieved complete regression of generalized lymphadenopathy and other systemic symptoms.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

not available

Details of Microscopic Findings

Core biopsy of axillary lymph node showed preserved architecture with dilatation of medullary sinuses and expansion of paracortex. Secondary lymphatic follicles demonstrated normal immunoarhitecture. In the paracortical area large aggregates of plasma cells were found (polytypic plasma cells).

No elements of malignant lymphoproliferative disease were found. Paracortical plasma cell proliferation with preserved lymph node architecture suggested a diagnosis of lymphadenitis, possibly associated with autoimmune disease, IgG4-related disease or Castleman disease, plasma cell variant.

Immunophenotype

Plasma cells demonstrated expression of CD138, and no expression of CD56 or CD20 by immunohistochemistry; less than 10% of plasma cells were IgG4 positive. No HHV-8 positive cells were found.

Cytogenetics

no

Molecular Studies

no

Proposed Diagnosis

Idiopathic multicentric Castleman disease (iMCD).

Interesting Feature(s)

In this case both major and four minor criteria required for the diagnosis of iMCD were met. Immunology workup showed no elements of systemic/inflammatory disease. This case emphasizes the importance of including iMCD in the differential diagnosis for the patients presenting with lymphadenopathy, systemic symptoms and paracortical plasma cell proliferation.

EA4HP24-LYWS-440

Lymphadenopathy with Marked IgG4+ Sheet-Like Plasma Cells (Favor IgG4-related LAD Over Plasma Cell Variant of Castleman Disease)

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Case Description

The patient is a 72 year old man, who underwent a left neck mass excision (4.3 x 3 x 1.5 cm). No clinical history or laboratory values were available at initial consultation.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

N/A

Details of Microscopic Findings

H&E sections show a markedly enlarged lymph node with many well-spaced follicles, some of which are hyperplastic and others are atretic. Focal "twinning" is noted. Large hyperplastic follicles and significant intrafollicular plasmacytosis are observed. Occasional regressed/atretic follicles display 'onion-skinning' pattern. Mild prominence of follicular dendritic cells is noted in some germinal centers. Vascularity is mildly increased. Within interfollicular regions, plasma cell numbers are variable, with many areas displaying 'sheet-like' increase in plasma cells. Immunoblasts are singly-dispersed (best seen by CD30 immunostain). Eosinophils are readily observed in multiple interfollicular foci. Focal PTGC is noted. Perivascular fibrosis and 'perifollicular granulomas' are observed.

Immunophenotype

Flow cytometry showed a CD4/CD8 ratio of 16.8, with no clonality on TRBC1. There is no support for a lymphoma, HHV8-related disease, luetic lymphadenitis, or indolent

lymphobplastic proliferation. No monotypic plasma cells were seen on kappa and lambda ISH stains. PTGC is highlighted by the combination of IgD, BCL2, CD20, CD23, and CD3 stains. PD1 staining was strong within intrafollicular cells, and only weak outside of lymphoid follicles. Interfollicular immunoblastic hyperplasia was highlighted by CD30, though no overtly malignant cells were seen. Negative stains include EBER, HHV8, spirochete/treponema, AFB, GMS.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Reactive lymphoid hyperplasia with significant increase in IgG4+ plasma cells, histopathologically favoring IgG4-related lymphadenopathy (over plasma cell variant of Castleman disease)

Interesting Feature(s)

Because of the sheet-like plasma cells (considered “grade 3,” if MCD), atretic follicles, GC twinning, and increased vascularity, idiopathic, HHV8-negative, plasma cell variant of multicentric Castleman disease was considered in this LN. Despite these overlapping histopathologic features with iMCD, however, the striking increased numbers of IgG4+ plasma cells in foci of nodal fibrosis, presence of eosinophils, and other IgG4-LAD features favor IgG4-LAD. The histopathology of the case demonstrates an admixture of features described in IgG4-related LAD: CD-like features, reactive follicular hyperplasia, interfollicular immunoblastic hyperplasia, PTGC, nodal fibrosis, and perifollicular granulomas. Dispersed scattered plasma cells on IgA stain appears to lend further support to IgG4-related-LAD. [Manabe A et al. Med Mol Morphol 2017;50:34-41]

On further consultant inquiry regarding patient’s clinical status, only limited history could be uncovered by referring pathologist, with only a recent point-of-care glucose level and surgical operative note for this lymph node excision available. Review of the patient's electronic medical record, there is no established autoimmune disorder. No recent CBCs, no other laboratory data (including no serum immunoglobulin levels), nor whole-body imaging studies were seen. Although clinical assessment is limited at this time, the paucity of clinical data suggests a very low likelihood of severe illness in this elderly patient and argues strongly against a diagnosis of multicentric Castleman disease, plasma cell variant. Rather, the combined clinical history (albeit limited) and histopathologic features favor an IgG4-LAD.

EA4HP24-LYWS-446

HHV-8 associated Multicentric Castleman disease

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Case Description

This is a lymph node excision (Oct 2014) from the left axilla of a 62 year-old man with generalized lymphadenopathy (strongly PET positive), fever and a rash. CRP was elevated (113 mg/L). He had been diagnosed with HIV the year before (2013). Despite therapy, he still had measurable viral loads (206 copies/mL). He was also HHV-8 positive. There were features of HLH: fever, high ferritin (856 µg/L), splenomegaly, pancytopenia [Hb 4.8 mmol/L, Plt 108 $x10^9$/L, Leuc 2.3 $x10^9$/L], high triglycerides (8.2 mmol/L) and hemophagocytosis in bone marrow aspirate.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

The lymph node shows an increase in follicles but with overall retention of architecture. The follicles are involuted with penetrating vessel. Some mantle zones show slight rimming of the lymphocytes. Both paracortex and medulla contain an increased amount of polytypic plasma cells. In between the follicles, there is an increase in high endothelial vessels.

Immunophenotype

The follicles are CD20 positive with BCL2 negative germinal centers. CD138 shows the increase in plasma cells. The plasma cells in the paracortex and medulla are polytypic for kappa and lambda, with predominance of kappa within normal range. In addition, the mantle zones contain lambda monotypic cells (plasmablasts). HHV-8 shows positive cells in the mantle zones (plasmablasts). EBER shows a few positive cells scattered throughout the paracortex.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

KSHV/HHV8-associated multicentric Castleman disease

Interesting Feature(s)

This is a typical example of an KSHV/HHV8-associated multicentric Castleman disease in an HIV positive patient. Patient was treated with rituximab/etoposide and got into complete metabolic remission on PT-CT. One year after treatment, his blood values were

completely normalized and there were no signs of recurrent disease. His HIV had been treated with cART with good response. Patient died at age 69 due to other causes without any signs of recurrent disease.
One could argue if the inflammatory signs are all due to the Castleman disease or if there is an associated HLH. Castleman disease is said to be one of the main causes of HLH. In this case, because of the only slightly elevated ferritin, the inflammation was regarded as part of the multicentric Castleman and not as (associated /secondary) HLH.

EA4HP24-LYWS-448

Castleman Disease

Dr. Tamar Guchash

Megalab, Pathology, Tbilisi, Georgia

Case Description
A 30-year-old otherwise healthy, immunocompetent woman referred to the hospital with symptoms of intestinal obstruction. According to abdominal CT scan results and surgical report unicentric ellipsoid mass forming lesion was excised from small intestinal mesentery for the purpose of routine morphological evaluation. A macroscopic sample was described as 4,4X4,3X3,1 sized well circumscribed, firm nodular growth which was partially enclosed with hyperemic layer of peritoneal tissue. On the cut surface of it well demarcated yellowish-brown structure with hemorrhagic areas was detected.
Biopsy Fixation Details
Tissue samples have been fixed approximately for 10 hours in 10% buffered formalin before and after macroscopic examination.
Frozen Tissue Available
Frozen unfixed specimens haven't been sent for intraoperative assessment.
Details of Microscopic Findings
Hematoxylin- Eosin-stained tissue sample showed centrally collagenous massively enlarged lymph node with prominent thick fibrous capsule and predominantly preserved architectural distribution. Secondary lymphoid follicles with variable shaped, including partially atretic germinal centers and circularly arranged lymphocytes of mantle zones were creating cortical zone of the node. Atretic follicular centers were traversed by a penetrating vessel. In between the follicular spaces on the background of hyalinized vascular structures and bands of fibrosis were detected.
Immunophenotype
CD23 revealed concentrically arranged follicular-dendritic cells with focal germinal center twinning. CD38 was positive in polytypic plasma cells without aggregate formation. HHV8 and IgG 4 immunohistochemical stains didn't show any positive cells in examined tissue. Assesment of Kappa Lambda light chain expresssion didn't show devitaion from the

normal ratio. CD20 + B cells and CD3+ T cells were distributed throuought the lymph node tissue in reactive pattern.

Cytogenetics

Not conducted

Molecular Studies

Not conducted

Proposed Diagnosis

HHV8 negative hyaline vascular unicentric Castleman Disease.

Interesting Feature(s)

Interesting morphological aspect of the case is prominent fibrotic bands and dense collagenous central areas, which could be related to stroma rich variant of Castleman disease.

EA4HP24-LYWS-452

HHV8-associated multicentric Castleman disease with plasmablastic aggregates

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Case Description

- 32-year-old male patient, with a clinical history of HIV and Kaposi sarcoma, presented with fever and lymphadenopathy.
- Lymph node core biopsy performed.

Biopsy Fixation Details

- 5% buffered formalin.

Frozen Tissue Available

- No.

Details of Microscopic Findings

- Effacement of nodal architecture.
- Lymphoid follicles are not readily apparent; there are areas of increased vascularity and prominent plasma cells.
- Focal aggregates of large atypical cells with round to ovoid, vesicular nuclei with frequently prominent nucleoli, interpreted to represent plasmablasts based on immunophenotypic characteristics.

Immunophenotype

- Large atypical cells express CD45 (majority), MUM1, HHV8, IgM, Lambda and MIB1; show variable weak expression of CD79a, BCL2 and BCL6; negative for CD20 (vast majority), PAX5, CD3, CD5, CD10, CD23, CD30 (vast majority), ALK and EBER (ISH).
- Associated plasma cell population shows mixed light chain and heavy chain expression.
- Normal lymphoid follicles are much reduced/virtually absent; however, CD20, CD79a and PAX5 demonstrate focal aggregates of small B-cells, with CD23 demonstrating occasional small condensed FDC meshworks, possibly representing atrophic lymphoid follicles.
- One of the plasmablastic aggregates appear to be co-located with a residual FDC meshwork.

Cytogenetics

- Not performed.

Molecular Studies

- Not performed.

Proposed Diagnosis

- HHV8-associated multicentric Castleman disease (MCD) with plasmablastic aggregates.

Interesting Feature(s)

- The plasmablastic aggregates are slightly larger and more prominent than one would typically expect to see in the setting of HHV8-associated MCD, and they appear to be proliferating independently of the lymphoid follicles.
- Although a diffuse sheet-like proliferation of plasmablasts is not seen in this material, unsampled areas of HHV8+ diffuse large B-cell lymphoma, not otherwise specified (HHV8+ DLBCL, NOS) cannot be entirely excluded. [endif]
- This case highlights the spectrum of changes that may be seen in HHV8-associated MCD, and the challenges in confidently defining progression to an HHV8+ DLBCL, NOS on a lymph node core biopsy. [endif]

EA4HP24-LYWS-455

Hyaline vascular Castleman's disease with dysplastic follicular dendritic cells and loss of FDC markers

Dr. Anna Green, Dr. Mina Mansy, Dr. Yurina Miki, **Dr. Mark Ong**

St Thomas' Hospital, Histopathology, London, UK

Case Description

- 62 year old female
- Multinodular goitre from 2013
- Presented in May 2020 with increasing left neck lump

- Ultrasound showed normal thyroid, but abnormal level 4 lymph node
- FNA of lymph node reported as suspicious for malignancy
- Core biopsy showed scattered large cells, of uncertain lineage
- Therefore excision biopsy performed

Biopsy Fixation Details

5% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

- Maintained follicular architecture, but follicles are small and have atretic germinal centres
- Focal hyalinisation and increased blood vessels
- Twinning of germinal centres present
- Germinal centres contain large cells suggestive of follicular dendritic cells, but some were morphologically atypical (large, pleomorphic, hyperchromatic nuclei)
- Similar cells present outside germinal centres

Immunophenotype

Immunohistochemistry

- Follicular dendritic cell markers difficult to interpret due to heavy staining of FDC meshworks
- Atypical cells outside the germinal centres were cyclin D1 positive and focally positive for CD21
- Negative: CD23, CD35, D2.40, EMA, CXCL13 and EGFR1
- Fascin and HLA-DR hard to interpret

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Hyaline vascular Castleman's disease with dysplastic follicular dendritic cells showing loss of FDC markers

Features not enough for FDC sarcoma

Interesting Feature(s)

- Hyaline vascular Castleman's disease with morphologically dysplastic FDCs
- These cells were negative for several FDC markers but were cyclin D1 positive, suggesting MAPK pathway activation
- FNA cytology was suspicious for malignancy
- Core biopsy was not conclusive despite Castleman's disease being considered as a differential

Panel Diagnosis Session I

Panel Diagnosis – Clinicopathological features of UCD with no associated FDC proliferation

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-101	UCD, HV stroma-rich variant	iTdT proliferation
EA4HP24-LYWS-53	UCD, PV with cytogenetic clonal aberration	Loss of D13S319
EA4HP24-LYWS-159	UCD, mixed type, stroma-rich	Progression to B-cell lymphoma 5 years later iTdT proliferation
EA4HP24-LYWS-185	UCD, mixed type	Interfollicular proliferation of monoclonal plasma cells IgA lambda
EA4HP24-LYWS-199	UCD,HV stroma-rich variant	3x relapse (over 20 yrs)
EA4HP24-LYWS-217	UCD, HV associated with thymoma	Association with thymoma, type AB
EA4HP24-LYWS-224	UCD,HV stroma-rich variant	---
EA4HP24-LYWS-235	UCD, HV	---
EA4HP24-LYWS-245	UCD, HV	iTdT proliferation
EA4HP24-LYWS-251	UCD, HV	Systemic symptoms in UCD, HV
EA4HP24-LYWS-261	CD, PLV with IgA restricted plasma cells associated with underlying plasma cell neoplasm	Clonal plasma cells in LN and presence of a systemic plasma cell neoplasm DD: LN infiltration of PC neoplasm with CD-like features
EA4HP24-LYWS-318	UCD, HV	Probable SRP72 gerline mutation
EA4HP24-LYWS-362	UCD, HV	---
EA4HP24-LYWS-426	UCD, HV	Extensive ossification
EA4HP24-LYWS-448	UCD, HV	---

Panel Diagnosis – Clinicopathological features of UCD associated with FDC proliferation/FDC sarcoma

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-73	FDCS associated with HV-CD	iTdT proliferation
EA4HP24-LYWS-271	UCD HV with atypical proliferation of FDC	Normal karyotype
EA4HP24-LYWS-369	UCD, HV with atypical stromal spindle cell proliferation	HIV+ patient iTdT proliferation
EA4HP24-LYWS-455	UCD, HV	Dysplastic FDCs with loss of FDC markers
EA4HP24-LYWS-147	FDCS associated with HV CD	TNFAIP3 K759fs*57 mutation
EA4HP24-LYWS-155	FDCS associated with HV CD	iTdT proliferation, Areas of HV CD, atypical FDC hyperplasia and FDCS
EA4HP24-LYWS-205	FDCS associated with HV CD	Areas of HV CD, atypical FDC hyperplasia and FDCS
EA4HP24-LYWS-260	FDCS associated with HV CD	Areas of HV CD, atypical FDC hyperplasia and FDCS
EA4HP24-LYWS-341	FDCS associated with HV CD	---

Panel Diagnosis – Clinicopathological characteristics of patients with iMCD NOS

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-20	iMCD NOS with elevated serum IgG4 and increased IgG4 + plasma cells	Borderline clinicopathological features between IgG4RD and iMCD NOS
EA4HP24-LYWS-273	iMCD, NOS with concurrent AA type amyloidosis + noncaseating granulomas	concurrent AA type amyloidosis + noncaseating granulomas
EA4HP24-LYWS-56	iMCD, NOS	4/5 criteria for TAFRO Monoclonal protein in urine: suspicious for POEMS
EA4HP24-LYWS-71	iMCD NOS with increased IgG4 positive plasma cells	Progression to cHL Polyclonal plasmacytosis >40% positive for IgG; > 100 IgG4 positive plasma cells /HPF
EA4HP24-LYWS-402	iMCD NOS with increased IgG4 positive plasma cells	---

EA4HP24-LYWS-439	iMCD, NOS	---

Panel Diagnosis – Clinicopathological characteristics of patients with TAFRO

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-153	iMCD, TAFRO	DD POEMS: polyneuropathy, hypothyroidism (but no plasma cell neoplasm)
EA4HP24-LYWS-10	iMCD, TAFRO	---
EA4HP24-LYWS-163	iMCD, TAFRO	HyperV morphology
EA4HP24-LYWS-249	iMCD, TAFRO	HyperV morphology
EA4HP24-LYWS-275	iMCD, TAFRO	Dg of iMCD, TAFRO with no LN biopsy: Masaki's criteria to be considered (3 major:anasarca, ↓Plt, systemic inflammation) and 2 minor
EA4HP24-LYWS-393	iMCD, TAFRO	---

Panel Diagnosis – Clinicopathological characteristics of patients with POEMS-associated MCD

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-326	POEMS-associated MCD	---
EA4HP24-LYWS-141	POEMS-associated MCD	---
EA4HP24-LYWS-257a	POEMS-associated MCD	After COVID 19 vaccinacion
EA4HP24-LYWS-257b	POEMS-associated MCD	After Covid-19 infection

Panel Diagnosis – Clinicopathological characteristics of patients with HHV8-associated MCD

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-103	KSHV/HHV8-associated MCD, with proliferation of highly atyp. HHV8+ cells: HHV8 +DLBCL vs extracavitary PEL	---
EA4HP24-LYWS-179	KSHV/HHV8-pos. Germino-tropic lymphoprolif. disorder with CD-like features	---

EA4HP24-LYWS-301	KSHV/HHV8-associated MCD	Aggregates of HHV8+ plasmablasts with IgH rearrangement
EA4HP24-LYWS-9	KSHV/HHV8-associated MCD	Aggregates of HHV8+ plasmablasts; fulminant course
EA4HP24-LYWS-28	KSHV/HHV8-associated MCD with atypical morphology	Purely follicular plasmablastic proliferation mimicking GLPD; EBER neg
EA4HP24-LYWS-48	KSHV/HHV8-associated MCD with concurrent KS	HIV negative, immunocompetent patient
EA4HP24-LYWS-68	KSHV/HHV8-associated MCD with concurrent KS	---
EA4HP24-LYWS-78	KSHV/HHV8-associated MCD with concurrent KS	HIV negative, immunocompetent patient
EA4HP24-LYWS-82	KSHV/HHV8-associated MCD with concurrent KS, splenic involvment	---
EA4HP24-LYWS-111	KSHV/HHV8-associated MCD with associated secondary HLH	HIV negative patient Development after Covid-19 infection
EA4HP24-LYWS-118	KSHV/HHV8-associated MCD with EBV+/HHV8+ LBCL (ePEL vs EBV+/HHV8+ DLBCL)	Diff.dg: ePEL vs EBV+/HHV8+ DLBCL
EA4HP24-LYWS-128	KSHV/HHV8-associated MCD with concurrent KS and EBV reactivation	---
EA4HP24-LYWS-143	KSHV/HHV8-associated MCD with EBV reactivation	Aggregates of HHV8+ plasmablasts; EBV-reactivation
EA4HP24-LYWS-146	KSHV/HHV8-associated MCD with subsequent PEL, EBV neg	EBV neg PEL in HIV+ setting
EA4HP24-LYWS-157	KSHV/HHV8-associated MCD with concurrent KS	HIV negative patient
EA4HP24-LYWS-171	KSHV/HHV8-associated MCD with concurrent KS	---
EA4HP24-LYWS-197	KSHV/EBV+DLBCL arising from HHV8+ MCD with associated KS	Diff.dg: ePEL vs EBV+/HHV8+ DLBCL
EA4HP24-LYWS-213	KSHV/HHV8-ass. MCD with con-current KS and EBV reactivation	---
EA4HP24-LYWS-225	KSHV/HHV8-associated MCD with concurrent KS	---
EA4HP24-LYWS-255	KSHV/HHV8-associated MCD with EBV reactivation	---
EA4HP24-LYWS-281	KSHV/HHV8-associated MCD	---

EA4HP24-LYWS-282	KSHV/HHV8-associated MCD with concurrent KS	Dispersed TdT-positive lymphocytes
EA4HP24-LYWS-300	KSHV/HHV8-associated MCD with concurrent KS	---
EA4HP24-LYWS-309	KSHV/HHV8-ass. MCD with con-current KS and histoplasmosis	---
EA4HP24-LYWS-334	HHV8+ DLBCL	IgM/λ negative; aberrant CD7 expression
EA4HP24-LYWS-342	KSHV/HHV8-associated MCD with EBV reactivation	---
EA4HP24-LYWS-381	KSHV/HHV8-associated MCD with EBV reactivation	Aggregates of HHV8+ plasmablasts; EBV reactivation
EA4HP24-LYWS-397	KSHV/HHV8-associated MCD with increased plasma cells	↑IgG4 plasma cells
EA4HP24-LYWS-446	KSHV/HHV8-associated MCD	---
EA4HP24-LYWS-452	KSHV/HHV8-associated MCD	Aggregates of HHV8+ plasmablasts

Panel Diagnosis – Clinicopathological characteristics of patients with CD-mimickers

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-325	Thymic cHL with CD-like features	---
EA4HP24-LYWS-62	FL with HV-CD features	Uncommon variant of FL
EA4HP24-LYWS-114	FL with HV-CD features	Uncommon variant of FL. Long lasting SAPHO syndrome
EA4HP24-LYWS-181	Bcl2-R-negative CD23+ FL with HV-CD features	Psoriatic arthritis on therapy with antirheumatic drugs and biologics
EA4HP24-LYWS-258	EMZL with CD-HV features	Cutaneous MZL 5 months previously
EA4HP24-LYWS-316	NMZL with focal CD-like features with IgG4 plasmacytic differentiation	---
EA4HP24-LYWS-169	EBV associated reactive hyperplasia with CD-like features and subsequent progression to cHL	immunocompetent person
EA4HP24-LYWS-99	LN with CD-like features + clonal IgM plasmocytosis, consistent with Schnitzler syndrome	LN in SS can morphologically mimic CD. Clonal rearrangement of IgH

		and IgK. MYD88 L265P mutation VAF8%
EA4HP24-LYWS-106	IgG4-related LAD with CD-like features (patterns 1,2 and 4)	---
EA4HP24-LYWS-312	IgG4-related LAD with CD-like features, (patterns 1,2,3)	---
EA4HP24-LYWS-390	IgG4-related LAD with CD-like features, (patterns 1,2)	---
EA4HP24-LYWS-434	IgG4-related LAD with CD-like features, pattern 1 and 5	---
EA4HP24-LYWS-440	IgG4-related LAD with CD-like features, all patterns (admixture of features)	---
EA4HP24-LYWS-332	FH with some CD-like features	IEI to be considered in regard to the clinical picture
EA4HP24-LYWS-385	KS in isolated LN with some CD-like features	Immunocompetent patient, incidentally found

LYMPHOMA SESSION II:
Atypical lymphoproliferations associated with germline or acquired genetic variants

Oral Presentations

EA4HP24-LYWS-252	Autoimmune Lymphoproliferative Syndrome in Adulthood: Navigating the Diagnostic Challenge between Atypical T-cell Proliferation and T-cell Lymphoma.
EA4HP24-LYWS-356	Immunodeficiency-associated polyclonal lymphoproliferation in the setting of activated PI3K-delta syndrome
EA4HP24-LYWS-436	EBV+ large B cell lymphoproliferation in an anal fissure uncovering X-linked lymphoproliferative disorder (XLP) in a 6-year-old boy.
EA4HP24-LYWS-119	EBV-positive B-cell Lymphoma in a Patient with XMEN Disease
EA4HP24-LYWS-29	Clonal Bronchopulmonary Lymphoplasmacytic Proliferation of Indeterminate Malignant Potential associated with Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)in a patient with Common Variable Immune Deficiency (CVID)
EA4HP24-LYWS-331	Patient with ATM germline mutation and multiple clonal B-cell proliferations.
EA4HP24-LYWS-189	Nodal T-follicular helper cell lymphoma and multiple concurrent EBV-positive B-cell lymphoproliferative disorders in a middle-aged man with a heterozygous germline *TET2* mutation.

EA4HP24-LYWS-252

Autoimmune Lymphoproliferative Syndrome in Adulthood: Navigating the Diagnostic Challenge between Atypical T-cell Proliferation and T-cell Lymphoma.

Dr. Fina Climent, Dr. Jan Bosch-Schips, Dr. Juan Azcarate, Dr. Xavier Solanich, Dr. Anna Esteve, Dr. Maria Rodriguez-Pinilla, Dr. Mar Varela, Dr. Montse Cortés, Dr. Eva Domingo

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Case Description

A 40-year-old man presented in March 2018 with cervical lymphadenopathy. A lymph node [LN] biopsy was taken (submitted) resulting in the diagnosis of Angioimmunoblastic T-cell Lymphoma [AITL], pattern II. Staging studies revealed generalized lymphadenopathies without involvement of the bone marrow (clinical stage III-A). The patient was treated with 6 cycles of CHOP, followed by autologous stem cell transplantation; the patient achieved complete remission.

In 2022, his daughter presented autoimmune thrombocytopenia and anemia and a diagnosis of Autoimmune Lymphoproliferative Syndrome [ALPS] was rendered. From that moment, the family was studied (see genealogical tree). The patient presented a FAS mutation (c.939del; p.ile314Serfs*47). With this information we reconsidered the diagnosis of the case.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

Yes

Details of Microscopic Findings

The LN architecture is preserved with a follicular hyperplasia, areas of atrophic follicles with Castleman-like features and a florid paracortical expansion. The paracortex presented a polymorphic and atypical lymphoid infiltrate with small lymphocytes mixed with blastoid cells, plasma cells and prominent endothelial venules.

Immunophenotype

The paracortex lymphoid cells are positive for T-cell markers CD3, CD2, CD5 and CD7 with expansion of double negative T-cells. TIA1 is positive and the proliferative index is high. Remarkably, in some areas of the lymph node there is an expansion of CD4 cells with expression of PD1. ICOS, CD10 and bcl6 are negative. CD21 staining revealed expanded follicular dendritic cells meshworks. Some blastoid cells are positive for CD30 and EBERs. The plasma cells are polytypic.

Cytogenetics

Not performed.

Molecular StudiesT-cell receptor (TR) gamma and beta (BIOMED-2) clonality analysis studies are polyclonal. NGS of TR is oligoclonal.
NGS (ThermoFisher panel) detected a FAS mutation (VAF 61%).

Proposed Diagnosis

ALPS-related T-cell lymphoproliferation.

Interesting Feature(s)

Lymphoid proliferation associated with ALPS in adult patients pose a diagnostic challenge. In our case, the following findings initially suggested that it could represent an early phase of AITL (pattern II): the clinical presentation was acute in onset, without a history of chronic lymphadenopathy; the histological pattern with a paracortical expansion of CD4 lymphocytes expressing PD-1; the disordered proliferation of follicular dendritic cells, along with the positivity for EBERS in some blastoid cells; clonality studies also indicated TR gamma monoclonality.
Duplicate clonality testing, along with the possibility of adding NGS for TR, confirmed the absence of clonality in the case, making it more consistent with T-cell proliferation. The option to complement the study of T-cell lymphoma cases with NGS (mutational landscape) is essential for reaching a diagnosis in these challenging cases.

EA4HP24-LYWS-356

Immunodeficiency-associated polyclonal lymphoproliferation in the setting of activated PI3K-delta syndrome

PhD/MD Emily F. Mason[1], Dr. Alexandra E. Kovach[2,3]

[1] *Vanderbilt University Medical Center, Department of Pathology, Microbiology, and Immunology, Nashville, USA;* [2] *Children's Hospital Los Angeles, Department of Pathology and Laboratory Medicine, Los Angeles, USA;* [3] *University of Southern California, Laboratory Medicine, Los Angeles, USA*

Case Description

A 14-year-old male with a clinical diagnosis of combined variable immunodeficiency (CVID) and a pathogenic germline variant in *PIK3CD* (p.Glu1021Lys) presented with 1 week of abdominal pain and nausea several weeks after international travel to Turkey. Complete blood count showed mild neutrophilia only. Abdominal imaging identified a 3.5-cm hypervascular solid mass arising from the cecum as well as bilateral mildly enlarged inguinal lymph nodes and mild splenomegaly. In the setting of known immunodeficiency, the constellation of findings was concerning for lymphoma, and an excisional lymph node biopsy and ileocecectomy were performed.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

None

Details of Microscopic Findings

The lymph node excision showed follicular hyperplasia. On gross examination, the ileocecal resection showed a 3.5-cm submucosal tan, firm, rubbery mass with mucosal ulceration, located at the appendiceal orifice, which grossly extended into the muscularis propria and showed a nodular cut surface. On microscopic examination, the mass was composed of hyperplastic lymphoid follicles with reactive germinal centers, which extended from the luminal surface, through the bowel wall and into the peri-colonic adipose tissue. The terminal ileum showed innumerable tan polyps on gross examination, which, on microscopic examination, were composed of hyperplastic Peyer's patches.

Immunophenotype

Flow cytometry performed on the ileocecal mass showed polytypic B cells with variably increased forward scatter properties and polytypic plasma cells. T cells showed retained expression of pan T-cell markers with heterogeneous CD57 expression and an increased CD4:CD8 ratio (14:1). Immunohistochemical stains for CD3, CD20, PAX5, and CD10 confirmed that the lymphoid follicles contained reactive germinal centers with underlying CD21-positive follicular dendritic meshworks. *In situ* hybridization for EBV-encoded RNA (EBER) and immunohistochemical stains for CMV and HHV8 were negative.

Cytogenetics

None

Molecular Studies

Broad-range PCR analysis was negative for fungal and mycobacterial-associated DNA.

Proposed Diagnosis

Immunodeficiency-associated polyclonal lymphoproliferation in the setting of activated PI3K-delta syndrome

Interesting Feature(s)

Certain primary immunodeficiencies, now termed inborn errors of immunity, may predispose to lymphoma. Benign lymphoid proliferations in this clinical setting are less well characterized. The phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (*PI3KCD*) gene encodes a subunit of the phosphatidylinositol 3-kinase (PI3K) enzyme. PI3K is expressed throughout leukocytes, including B and T cells, and helps regulate their differentiation and proliferation. Autosomal dominant gain-of-function mutations in *PI3KCD* underlie PI3K-delta syndrome, a condition characterized by recurrent viral and bacterial infections and a mimic of CVID. Another hallmark of PI3K-delta syndrome is systemic benign lymphoid hyperplasia related to the dysregulated lymphocyte proliferation in this condition. In this dramatic case, benign hyperplasia of resident lymphoid tissue in the cecum and terminal ileum mimicked Burkitt lymphoma and required surgical resection. The lymphoproliferation was hypothesized to have been triggered by subclinical infection, possibly related to recent international travel. The patient is currently 5.5 years status-post surgical resection and is receiving PI3K-delta inhibitor therapy, with no evidence of recurrent lymphoproliferation.

References (PMIDs): 31402502; 28972011; 29535736; 26371693; 26406182; 34692603

EA4HP24-LYWS-436

EBV+ large B cell lymphoproliferation in an anal fissure uncovering X-linked lymphoproliferative disorder (XLP) in a 6-year-old boy.

Dr. Rossella Sarro[1,2], PhD/MD Bettina Bisig[2], Dr. Carole Gengler[2], Prof. Christine Sempoux[2], Prof. Laurence de Leval[2]

[1] Ente ospedaliero cantonale, Institute of Pathology EOC, Locarno, Switzerland; [2] University Hospital Lausanne (CHUV), Institute of Pathology, Lausanne, Switzerland

Case Description

A 6-year-old boy, known for hypoacusia due to chronic otitis and adenoidectomy, was suspected clinically of Crohn's disease. Excision of an anal fissure examined at an outside laboratory was reported as mucosal fissure with non-specific but unusually intense submucosal inflammatory reaction (***sample 1, submitted to the workshop***). Four months later, gastrointestinal biopsies were sent to another outside institution and concluded as acute colitis with mild lymphoid hyperplasia and rectal ulcer with clonal blastic B-cell proliferation, with a differential diagnosis of a reactive process *versus* early lymphoma (sample 2). Local therapy (mesalazine and corticosteroids) was administered. Unfavourable evolution with perianal tumefaction, weight loss and cachexia led to a second coloscopy. No mucosal abnormalities were seen except in the rectal/anal area where biopsies were repeated 6 months from the initial samples. They showed an anal canal mucosal ulceration associated with a monoclonal EBV+ large B-cell lymphoproliferation, consistent with DLBCL (sample 3). Upon review of the series of samples, we concluded that DLBCL was already present in sample 1 and 2. EBV was detected in the peripheral blood (26'600 copies/mL). Immunologic analysis uncovered agammaglobulinemia, treated with regular Ig perfusions. After staging (stage II), he was started on chemotherapy. An allogeneic hematopoietic stem cell transplantation (HSCT) was performed. The patient was in complete remission at last follow up (18 months from the initial diagnosis).

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

At the anorectal mucocutaneous junction, presence of large sheets of lymphoid cells with blastic (immune- / centroblastic) aspect, with large nuclei, irregular contours, vesicular chromatin and one or more variably prominent nucleoli. Some cells presented a Hodgkin/Reed-Sternberg (HRS)-like aspect. Small lymphocytes were intermixed, without visible plasma cells. Focal micro-vascular fibrinoid necrosis. No granuloma nor pathogens detected on PAS and Giemsa stains.

Immunophenotype
The large atypical cells were CD20+, PAX5+ (faint), CD5-, CD23-, CD10-, BCL2+, BCL6+ (diffuse), MUM1+ (partial), MYC -/+ (20-30%), with a Ki67>70%. CD30 was positive in scattered large cells. Numerous intermingled T cells (CD3+) and histiocytes (CD68+). No follicular dendritic meshwork was associated. No plasma cells (CD138) were identified. No CMV detected.
Cytogenetics
ND.
Molecular Studies
ISH for EBV (EBERs): positive in a large proportion of the large cells.
FISH: No *BCL2, BCL6 or MYC* gene rearrangement.
Clonality analyses: monoclonal IG gene rearrangement, identified in sample 1 and 3 (excision and biopsies 6 months later).
Germline analysis (NGS): pathogenic mutation (c.192G>A) in *SH2D1A* gene, known to cause X-linked lymphoproliferative disorder (XLP).
Proposed Diagnosis
Acute colitis/ulcerated proctitis with **monoclonal EBV+ large B-cell lymphoproliferation, consistent with EBV+ DLBCL, associated to XLP (ICC) /DLBCL, EBV+, IEI-associated (Inborn error of immunity, XLP) (WHO).**
Interesting Feature(s)
We describe an unusual and difficult case of pediatric anal canal/rectal ulcerated lesions associated with an EBV+ large cell lymphoproliferation. While some features raised the possibility of an EBV+ mucocutaneous ulcer (MCU), the condition was best diagnosed as DLBCL. Despite some HRS-like cells the presence of a mass and large sheets of blasts already qualified for DLBCL. Low to absent intramucosal plasma cells allowed to uncover an underlying XLP. HSCT is intended to cure both the lymphoma and the IEI.

EA4HP24-LYWS-119

EBV-positive B-cell Lymphoma in a Patient with XMEN Disease

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Mass General Brigham, Department of Pathology, Boston Children's Hospital, Boston, USA

Case Description
A 19-year-old man was referred to our institution for workup of stroke in the setting of Varicella Zoster (VZV) encephalitis. His past medical history included recurrent ear infections, molluscum contagiosum, fungal esophagitis, oral cold sores, hypogammaglobulinemia (receives weekly IVIG), and appendicitis. Mediastinal and axillary lymphadenopathy were noted during the admission for VZV encephalitis. Biopsies

of lymph nodes showed atypical features including regressed follicles with expanded mantle zones, and a few scattered cells were positive for EBV-encoded RNA (EBER) in-situ hybridization (ISH). Immunologic and genetic studies were sent for evaluation of primary immunodeficiency. Peripheral blood EBV PCR showed >3 million copies of EBV genome/mL. MRI demonstrated a 2.2 cm right palatal lesion which was moderately intense on T2-weighted imaging. A biopsy of the palatal lesion was performed.

Biopsy Fixation Details

A 0.4 cm mucosal/submucosal biopsy specimen was received in 10% neutral buffered formalin along with three additional tissue fragments, which were submitted entirely for histology.

Frozen Tissue Available

The tissue was not frozen.

Details of Microscopic Findings

Histologic sections demonstrated squamous mucosa with underlying minor salivary gland tissue and sheet-like atypical lymphoid infiltrate composed predominantly of small cells with irregular nuclei, condensed chromatin, and scant to moderate pale cytoplasm. Increased plasmacytoid cells with abundant cytoplasm and frequent Dutcher bodies were noted.

Immunophenotype

Immunostains showed that the infiltrate was composed of CD20-positive CD79a-positive B cells, negative for CD43. The plasmacytoid cells demonstrated CD79a expression, partial CD20, negative CD138, and monotypic lambda light chain restriction by kappa and lambda ISH. EBER was diffusely positive. CD21 showed disrupted follicular dendritic cell meshwork in the background of the infiltrate. Ki67 proliferation index was ~20%. HHV8 was negative.

Cytogenetics

Cytogenetics was not performed.

Molecular Studies

Molecular diagnosis was not performed on tissue biopsy specimen. However, given the history of recurrent infections, VZV encephalitis, atypical lymph node pattern on biopsy, and low IgG levels, an NGS panel for germline primary immunodeficiency was performed which showed a hemizygous MAGT1 deletion (exon 9), consistent with X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (XMEN) disease.

Proposed Diagnosis

EBV-positive B-cell lymphoma with plasmacytic differentiation, with features suggestive of EBV-positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

Interesting Feature(s)

XMEN disease is an X-linked combined primary immunodeficiency caused by a mutation in the gene Magnesium transporter 1 (MAGT1) on chromosome Xq21.1. It is characterized by CD4 lymphopenia, severe viral infections, and defective T-cell activation. These patients are susceptible to EBV infections and EBV-driven lymphomas. Since 2011, only about 45 cases have been described in the medical literature. About 30 pathogenic/likely pathogenic variants of MAGT1 gene have been described, mostly point mutations leading to loss-of-function variants. These variants include 12 stop-gain, 10 frameshift, 2 splicing, and 2 missense variants, and 4 large exon deletions in the MAGT1 gene. Exon 9 MAGT1 deletion

was considered likely pathogenic given the patient's clinical features, EBV+ lymphoma, and similarity to described pathogenic variants, which predominantly include loss of function null (stop and frameshift) variants, including in exon 9, and other exon deletions.

EA4HP24-LYWS-29

Clonal Bronchopulmonary Lymphoplasmacytic Proliferation of Indeterminate Malignant Potential associated with Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)in a patient with Common Variable Immune Deficiency (CVID)

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Case Description

The patient is a 52-year-old man with a history of common variable immune deficiency (CVID) with a heterozygous *TNFRSF13B*, c.310T>C (p.Cys104Arg) mutation. He presented with an 11-year history of worsening solid and groundglass pulmonary nodules (largest 1.8 cm) and bulky hilar lymphadenopathy. Several small biopsies were unrevealing of a neoplastic process; therefore a lung wedge resection was performed. The resection showed changes consistent with Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) and an associated lymphoplasmacytic proliferation that was lambda restricted by in situ hybridization (ISH), lambda skewed by flow cytometry, and clonal for *IGH* gene rearrangement by PCR. Based on the findings, we rendered a diagnosis of extranodal marginal zone lymphoma; however, the case was sent to the National Institutes of Health (NIH) for a second opinion and the expert consultant favored a benign/reactive process. Per the NIH report, the overall findings were felt to be classic for CVID-associated benign lung changes without clear evidence of lymphoma. The excess of lambda expression was acknowledged; however, it was emphasized that atypical marginal zone proliferations in the lung associated with CVID are well known, which can be transient and do not always progress to lymphoma. The patient was treated with IVIG and Rituximabx4 for GLILD, and repeat imaging showed marked improvement in the lung nodules and lymphadenopathy. The patient remains in remission eight months later.

Biopsy Fixation Details

10% Neutral-Buffered Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The lung parenchyma showed variably distributed ill formed non-necrotizing granulomas, multinucleated giant cells, focal interstitial fibrosis, follicular bronchiolitis, and lymphocytic interstitial pneumonitis. In addition, a dense peribronchiolar nodular and focally diffuse lymphoid infiltrate was present comprised of small mature lymphocytes and plasmacytoid cells. Immunohistochemistry showed several well-formed peribronchiolar B-cell follicles with largely retained underlying meshworks. The interfollicular zones showed abundant T cells and occasional plasmacytoid cells. The plasmacytoid cells were lambda restricted by kappa & lambda ISH. The B cells and plasmacytoid cells were negative for CD5, CD10, BCL6, CD43, cyclin-D1, and LEF1. EBER ISH was negative.

Immunophenotype

Flow cytometry performed on the lung tissue revealed a lambda light chain skewed B-cell population (kappa:lambda ~0.4) that was positive for CD19, CD20, CD22, partial CD23, partial CD200, & partial CD38, while negative for CD5, CD10, and CD25.

Cytogenetics

N/A

Molecular Studies

Positive for clonal *IGH* rearrangement

Negative for *MYD88* L265P mutation

Proposed Diagnosis

Original diagnosis: Extranodal marginal zone lymphoma arising in a background of GLILD

NIH: Bronchogenic lymphoid infiltrate with focal granulomatous inflammation and mild plasmacytosis with excess lambda light chain expression

Interesting Feature(s)

Patients with CVID can harbor clonal lymphoid populations in their tissues, particularly in association with GLILD, making the distinction from MALT lymphoma challenging. Studies have shown that these clonal populations can be transient and may not always progress to overt lymphoma. In the setting of GLILD, the detection of these populations makes the distinction from MALT lymphoma very challenging. Given that the first line therapy for both GLILD and pulmonary marginal zone lymphoma is anti-CD20 monotherapy, the malignant potential of these populations remains uncertain and can only be determined after long term clinical follow up.

EA4HP24-LYWS-331

Patient with ATM germline mutation and multiple clonal B-cell proliferations.

PhD/MD Ivonne A. Montes-Mojarro, Dr. Antonio Vogelsberg, Prof. Leticia Qintanilla-Martinez, Prof. Falko Fend

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Case Description

A 16-year-old male, clinically diagnosed with ataxia-telangiectasia (A-T), manifested by cerebellar ataxia, oculomotor apraxia and telangiectasias, among others, presented with a restrictive ventilatory defect and chronic sinusitis, splenomegaly, and ubiquitous lymphadenopathy associated with combined immunodeficiency on 4-week immunoglobulin substitution. Peripheral blood analysis revealed lymphopenia. A retroauricular lymph node biopsy was performed (submitted biopsy). 4 months later, a right kidney mass was discovered and diagnosed as diffuse large B-cell lymphoma (not submitted). The patient was treated with dexamethasone and 4 cycles of rituximab. Remission was achieved, but the patient developed therapy-related neuropathic pain.

Biopsy Fixation Details

Retroauricular lymph node biopsy of formalin-fixed paraffin embedded tissue.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Effacement of the lymph node architecture by a diffuse proliferation composed of mostly small to medium-sized lymphoid cells, extensive plasma cells in various stages of maturation, some multinucleated, some with dutcher bodies, as well as scattered centroblasts, immunoblasts and multiple granulomas.

Immunophenotype

MUM1 highlighted the plasma cell component with IgM expression and lambda light chain restriction, but negativity for IgG, IgA, CD56 and cyclin D1. CD30 staining displayed numerous blasts but no clear atypical cells. CD20 highlighted a dense subcapsular and scattered medullary B-cell population lacking organization. EBER in situ hybridization was negative. Interspersed reactive CD3+, CD4+ T cells.

Cytogenetics

Not done.

Molecular Studies

IGH clonality analysis demonstrated clonal peaks of 289 (FR2) and 146 (FR3) bp. Targeted next generation sequencing of 78 genes frequently altered in lymphoma revealed two mutations in *ATM* (splicesite_5, VAF 54% and p.C1366*, VAF 48%). Clonality analysis of the diffuse large B-cell lymphoma diagnosed 4 months later showed different clonal peaks.

Proposed Diagnosis

Retroauricular lymph node with an atypical clonal B-cell lymphoproliferation with plasma cell differentiation EBV negative versus marginal zone lymphoma (MZL) with marked plasmacytic differentiation.

Interesting Feature(s)

- This is a rare case of a patient who developed an indolent and an aggressive clonally unrelated clonal B-cell proliferation in the context of A-T. About 10–15% of A-T patients develop a malignancy in the first two decades of life, such as acute leukemias, Hodgkin lymphomas and non-Hodgkin lymphomas, mainly aggressive B-cell NHL (Suarez et al. JCO 2015).
- ATM is involved in DNA damage response. The classical phenotype of A-T results from the presence of null mutations in *ATM*, leading to loss of function. Milder phenotypes are related to splice site mutations allowing expression of some transcript (Taylor et al. J Clin Pathol 2005). This case exemplifies an incomplete A-T genotype.
- Immunodeficiency-associated B-cell lymphoproliferative disorders (IA-B-LPDs) comprise a wide spectrum of lesions, including polymorphic LPDs, aggressive lymphomas and, rarely, indolent lymphomas. The overlapping features between MZL and a clonal polymorphic B-LPD observed in this case emphasize the difficulty in classification (Yasodha et al. Blood 2018).
- EBV-negativity is rare and reported in only 20-40% of IA LPDs, underlining the role of other non-EBV driving factors in the pathogenesis of these clonal LPDs (Swerdlow SH et al. WHO 2017). A major defect in the regulation of B-cell ontogeny is also stressed by the subsequent development of an aggressive B-cell lymphoma.

EA4HP24-LYWS-189

Nodal T-follicular helper cell lymphoma and multiple concurrent EBV-positive B-cell lymphoproliferative disorders in a middle-aged man with a heterozygous germline *TET2* mutation.

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Case Description

A 59 y/o man with a h/o CAD was found to have diffuse LAD. Biopsy of a cervical LN (cLN) was interpreted as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). The patient received R-CHOP and achieved complete remission. Two years later, the patient was diagnosed with nodal T-follicular helper cell lymphoma (nTFHcL), AITL subtype in the lung, spleen, axillary LN (aLN), and bone marrow (BM). Concurrently, two distinct EBV+ B-

cell lymphoproliferative disorders with plasmacytic differentiation were also identified - a lambda+ LPD in the lung and a kappa+ LPD in the spleen and aLN. The patient was treated with belinostat and azacitidine and remains stable 1.5 yrs after the T- and B-cell lymphoma diagnoses.

Biopsy Fixation Details

LN measuring 3.8 x 2.8 x 2.5 cm fixed in formalin.

Frozen Tissue Available

Yes

Details of Microscopic Findings

The aLN is highlighted in this submission and shows features consistent with nTFHcL, AITL subtype. Outside of the residual B-cell follicles, an atypical pleomorphic B-cell infiltrate with plasmacytic differentiation is present. Abundant epithelioid histiocytes are present.

Immunophenotype

Neoplastic T-cells: CD3+, CD2+, CD5+, CD7(weak)+/-, CD4+, PD1+, CD10+/-, BCL6+/-, MUM1-.
Neoplastic B-cells: CD20+, CD79a+, CD30+/-, kappa(ish)+, lambda(ish)-, EBER(ish)+.

Cytogenetics

T-cell clone: t(1;14)(q21;q11.2); TCR alpha/delta rearrangement: 30.8%.
B-cell clone: t(1;14)(q21;q32); IGH rearrangement: 10%.

Molecular Studies

NGS studies performed on the cLN, lung, spleen, aLN, and BM showed the following mutations:
TET2 (p.E1320Dfs): Germline, present in all specimens, confirmed on buccal swab.
TET2 (p.I1177S): cLN 8%, lung 19%, spleen 29%, aLN 35%, BM 5%.
PPM1D (p.N448Ifs): cLN 9%, lung 24%, spleen 34%, aLN 40%, BM 45%.
NOTCH3 (p.A1802Gfs): lung 13%.
TRB and IGH gene rearrangement by PCR, performed on all specimens:
TRB: 257 VBA-JB1 & 304 DB1-JB1 in lung, spleen, aLN, BM, but not in cLN. cLN is polyclonal.
IgH: 312 FR1& 248 FR2 in lung. 264 FR2 & 122 FR3 in spleen and aLN. cLN and BM are polyclonal.

Proposed Diagnosis

Nodal T-follicular helper cell lymphoma, angioimmunoblastic type, and concurrent EBV-positive B-cell lymphomas with plasmacytic differentiation associated with heterozygous germline TET2 mutation.

Interesting Feature(s)

TET2 is one of the most common somatically mutated genes in hematopoietic malignancies; however, germline *TET2* mutations are rarely reported. To date, it has been described in six families- four with at least one T-cell malignancy and four with B-cell malignancy. Since somatic *TET2* mutations are known to be initiating events in nTFHcL and seen in concurrent nTFHcL-associated B-cell LPDs, the germline *TET2* mutation likely contributes to our patient's complex diseases. Immunodeficiency may also play a role in our patient's EBV+ B-cell LPDs. However, whether the immunodeficiency is secondary to the germline *TET2* mutation or has resulted from the nTFHcL remains to be determined. Of note, four of the previously described families demonstrated immunodeficiency and/or autoimmune features.

It remains uncertain if germline *TET2* mutations are under-recognized, given that *TET2* is not included in most sequencing panels for predisposition to hematopoietic malignancies. While some families with germline *TET2* mutations present early in life, others develop neoplasms later in life, which may not raise suspicion for germline predisposition. In summary, our case demonstrates an association between germline *TET2* mutation and the development of multiple lymphoid malignancies and underscores the potential benefits of including *TET2* in hereditary genetic testing panels.

Cases Discussed by the Panel

EA4HP24-LYWS-5	Near (CD5+) ETP-ALL in the context of Nijmegen breakage syndrome
EA4HP24-LYWS-7	Waldenstrom Macroglobulinaemia and Myelodysplastic Neoplasm with DDX41 mutation
EA4HP24-LYWS-12	Fulminant Epstein-Barr virus lymphadenitis due to X-linked lymphoproliferative disease
EA4HP24-LYWS-37	Atypical lymphoproliferation of the thyroid due to germline-derived *ATM*-mutation potentially causing a disturbed germinal centre reaction
EA4HP24-LYWS-42	Autoimmune Lymphoproliferative Syndrome
EA4HP24-LYWS-43	·Lymphoproliferative EBV positive disease with morphologic features resembling follicular lymphoma high grade (Grade 3a)
EA4HP24-LYWS-49	Nodular Lymphocyte Predominant Hodgkin Lymphoma Arising in Autoimmune Lymphoproliferative Syndrome: T cells, Histiocytes and FAS
EA4HP24-LYWS-66	Autoimmune lymphoproliferative syndrome (ALPS) with features of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman Disease)
EA4HP24-LYWS-75	T-cell large granular lymphocytic leukemia (T-LGLL) in the context of likely somatic*GATA2* mutation
EA4HP24-LYWS-108	Sequential T-lymphoblastic lymphoma and diffuse large B-cell lymphoma, NOS, arising in a child with ataxia telangiectasia.
EA4HP24-LYWS-130	Incidental B-lymphoblastic lymphoma in a risk reducing bilateral salpingo-oophorectomy for BRCA1 germline mutation
EA4HP24-LYWS-162	Monocytoid B cell hyperplasia progressing to nodal marginal zone lymphoma with associated polymorphous EBV component in a child with CVID
EA4HP24-LYWS-166	Atypical plasmacytic and immunoblastic proliferation in a lymph node from a Wiskott-Aldrich patient
EA4HP24-LYWS-177	Inborn Error of Immunity (ITK mutation)-associated Lymphoproliferative Disorder, classic Hodgkin lymphoma, EBV+.
EA4HP24-LYWS-178	Inborn Error of Immunity (NKD)-associated Lymphoproliferative Disorder, EBV+ with Hodgkin-like Features.
EA4HP24-LYWS-180	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) arising in association with a T-cell rich reactive lymphoid hyperplasia in a patient with activated PI3Kδ syndrome
EA4HP24-LYWS-184	*Atypical lymphoproliferation and massive fatal hemophagocytosis in an EBV-positive patient with homozygous mutation in the RAB27A*
EA4HP24-LYWS-200	Relapsed classic Hodgkin lymphoma; when to suspect an underlying inborn error of immunity

EA4HP24-LYWS-207	Kabuki syndrome induced common variable immunodeficiency (CVID)
EA4HP24-LYWS-214	Recurrent florid marginal zone hyperplasia
EA4HP24-LYWS-222	A 64 year old male presenting with autoimmune hemolytic anemia and lymphadenopathy progressing to large B-cell lymphoma over a period of 2.5 years with a germline mutation in PIK3R1.
EA4HP24-LYWS-231	Spectrum of Atypical lymphoid proliferations in a Patient with Activated Phosphoinositide 3-Kinase δ Syndrome 2
EA4HP24-LYWS-284	Incidental XLP discovery leading to Burkitt-like lymphoma in a 10-year-old male
EA4HP24-LYWS-285	EBV positive lymphoma and chronic EBV infection in a patient with ataxia telangiectasia
EA4HP24-LYWS-288	Mutation in the perforin gene inducing a macrophage activation syndrome
EA4HP24-LYWS-295	Recurrent EBV+ diffuse large B-cell lymphoma in a patient with tubular aggregate myopathy muscular dystrophy and associated primary immunodeficiency disorder
EA4HP24-LYWS-299	EBV+ T-cell lymphoproliferative disorder in a paediatric patient with germline*TNFAIP3* mutation and Pompe disease.
EA4HP24-LYWS-305	An unusual tonsil lymphoproliferation
EA4HP24-LYWS-329	EBV-positive Burkitt Lymphoma in the setting of CVID
EA4HP24-LYWS-336	Atypical polymorphous lymphoproliferative disorder involving a spinal epidural mass in the setting of CTLA4 haploinsufficiency
EA4HP24-LYWS-365	EBV-related proliferations (reactive hyperplasia and lymphoproliferative disorders) in a patient with common variable immuodeficiency (CVID)
EA4HP24-LYWS-389	Peripheral T-cell lymphoma, not otherwise specified associated with *TET2* germline variant with mosaicism.
EA4HP24-LYWS-413	Atypical B-cell proliferation in a patient with germline RAG2 variant
EA4HP24-LYWS-418	EBV-positive B cell lymphoproliferative disorder presenting with systemic and digestive disease in a patient with an Activated phosphoionositide-3 kinase delta syndrome (APDS)
EA4HP24-LYWS-425	Bone marrow findings of autoimmune lymphoproliferative syndrome
EA4HP24-LYWS-438	Bilateral conjunctival marginal zone lymphoma in a prepubescent child with constitutional CTLA4-mutation
EA4HP24-LYWS-450	Necrotizing Lymphadenitis in the setting of Atypical Germline GATA2 Mutation

EA4HP24-LYWS-5

Near (CD5+) ETP-ALL in the context of Nijmegen breakage syndrome

Dr. Thomas R. Oliver[1], Dr. Liz Hook[1,2], Dave Bloxham[3], Prof. Nicholas Coleman[1,4], **Dr. Joy Staniforth**[3]

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Case Description

A male patient around 10 years of age presented with generalised lymphadenopathy, approximately a year after completing maintenance chemotherapy for T-lymphoblastic leukaemia that had been diagnosed two years prior to presentation. A preceding diagnosis of T-cell non-Hodgkin lymphoma had been made at a few years of age and had been treated with high-intensity chemotherapy.

The above two prior diagnoses were made by other institutions, and diagnostic reports were not available via UK records. The patient also had a diagnosis of Nijmegen breakage syndrome that had been made through genetic testing.

Biopsy Fixation Details

Fresh lymph node tissue was mechanically disaggregated to provide a single cell suspension for flow cytometric evaluation. Fresh bone marrow aspirate material was used for morphological and flow cytometric evaluation as well as cytogenetic and molecular assessments (described below); DNA and RNA was stored. The lymph node excision and bone marrow trephine samples were fixed in 10% NBF. The bone marrow biopsy underwent EDTA decalcification.

Frozen Tissue Available

Yes, stored to enable whole-genome sequencing if indicated.

Details of Microscopic Findings

Bone marrow and lymph node replacement by predominantly medium-sized, relatively monomorphic lymphoid cells showing high nuclear:cytoplasmic ratios, and ovoid to slightly indented nuclei, even chromatin, and variably visible nucleoli.

Immunophenotype

Positive: CD45 (weak), CD34, CD2, cytoplasmic CD3, CD5, CD7 (strong), CD10 (weak), CD99, HLA-DR, TdT, CD11b (weak), CD13, CD33 (moderate), CD56 (strong), CD79a (subset; weak variable).

Negative: CD1a, surface CD3, CD4, CD8, CD20, CD19, MPX, CD117.

Cytogenetics

Performed on bone marrow aspirate sample.

Microarray: clonal copy number loss of Xq26.2-q26.3 and 12p13.33-p12.2 and clonal copy number gain of 2q13, 9q34.12-q34.13 and 13q31.1-q34.

FISH:
~15% of cells showed either a partial duplication of the *ABL1* region, or a variant or an unbalanced rearrangement involving *ABL1*. ~11% showed a loss of one *ETV6* signal(12p13), but no conclusive evidence of an *ETV6* rearrangement.
No *BCR::ABL1* t(9;22) rearrangement, nor *FIP1L1::PDGFRA* (4q12), *TCF3(E2A)::PBX1* t(1;19)(q23;p13) or *TCF3(E2A)::HLF* t(17;19)(q22;p13) rearrangements.
No evidence of rearrangement of *KMT2A (MLL)* (11q23), *TLX3* (5q35), *TRA/TRD* (14q11), *TRB* (7q34), *TRG* (7p14), *ABL2* (1q25.2) or *PDGFRB* (5q32).
No evidence of deletion of *CDKN2A* (9p21).

Molecular Studies

RNA Fusion Panel (Illumina TruSight): *NUP214::ABL1* fusion detected.

Proposed Diagnosis

Near (CD5+) early T-precursor acute lymphoblastic leukaemia (near ETP-ALL)

Interesting Feature(s)

The diagnosis of near ETP-ALL as well as two concurrent T-cell lymphoma diagnoses is uncommon in Nijmegen breakage syndrome.
(A case of ETP-LBL in NBS was presented by K Brannock, S Kahwash at the SH-EA4HP November 2023 meeting as case SH2023-124; no other examples of ETP-ALL/LBL nor near ETP-ALL/LBL exist in the literature to the best of our knowledge.)

EA4HP24-LYWS-7

Waldenstrom Macroglobulinaemia and Myelodysplastic Neoplasm with DDX41 mutation

Dr. Laura Chen, Dr. Samar Issa

Middlemore Hospital, Auckland, New Zealand

Case Description

65M
Background: increased alcohol consumption and cirrhosis
Diagnosed with Waldenstroms Macroglobulinaemia 2016
Presented with anaemia and thrombocytopenia with IgM monoclonal band of 25g/L.
Initial bone marrow showed involvement with low disease burden with no evidence of myelodysplasia. MYD88 mutation positive
Started treatment RCD (rituximab /cyclophosphamide/ dexamethasone) in 2017 because of progressive cytopenias. Bone marrow disease burden at the time 50-60% lymphocytes. CT body – no significant lymphadenopathy or splenomegaly. Significant treatment delays because of prolonged cytopenias and hyponatraemia – thought to be secondary to increased alcohol intake. Completed 6 cycles April 2018 – achieved good partial response to treatment. Bone marrow burden 50-60% -> 10-20%. IgM paraprotein 25g/L -> 6g/L
Evidence of disease progression in 2021 with paraprotein 6g/L ->13g/L. Repeat bone

marrow biopsy 10/9/20. De novo myelodysplastic syndrome with multilineage dysplasia – new since previous end of treatment bone marrow in 2018. Residual Waldenstoms Macroglobulinaemia – disease burden 25%. Normal cytogenetics. Watchful waiting
Bone marrow biopsy repeated 2/2/23 for progressive anaemia and persistent severe neutropenia. Stable myelodysplastic features. Lymphoplasmacytic lymphoma disease burden 30-40%. Normal cytogenetics. Myeloid NGS showed likely germline DDX41 mutation - see below.
Further testing to confirm germline mutation not requested as no biological family

Biopsy Fixation Details

FFPE

Frozen Tissue Available

no

Details of Microscopic Findings

Blood film: Hb 86g/L, MCV 113fL. Platelets 133x10E9/L, neutrophils 1.8x10E9/L, blasts 0.05x10E9/L
Bone marrow aspirate: Normocellular erythropoiesis with normoblastic and megaloblastic maturation. Dysplastic features in 20-30% with multinucleation, cytoplasmic vacuolation, abnormal haemoglobinisation and megaloblasts. Rare ring sideroblasts <15%. Normocellular granulopoiesis with sequential maturation, dysplasia seen in <10% with mostly abnormal granulation. No increase in blasts. Reduced megakaryopoiesis. Lymphocytes are increased 39% -small mature forms.
Bone marrow trephine: Normocellular trephine with increased B lymphocytes 30-40%. Normocellular erythropoiesis, reduced granulopoiesis and increased megakaryopoiesis with significant dysplastic features; numerous small hypolobated forms and micromegakaryocytes accounting for 30%.

Immunophenotype

Two clonal populations of B-cells, both negative for CD10 and CD5, one with a brighter CD19 and lambda positive and the second one with a dimmer CD19 and kappa positive. Both populations are of similar size.

Cytogenetics

46,XY[20]

Molecular Studies

·Myeloid NGS – performed at Grafton Clinical Genomics, Auckland University
·DDX41 G173R; VAF48% - likely germline, likely pathogenic
·DDX41 G530D; VAF 19% - Somatic; oncogenic
·MYD88 L252P; VAF 8% - Somatic; oncogenic
·BCORL1 A409Gfs*7; VAF 8% - Somatic; oncogenic

Proposed Diagnosis

Lymphoplasmacytic lymphoma – Waldenstroms Macroglobulinaemia subtype diagnosed 2016 (ICD-O code: 9671/3)
Myelodysplastic neoplasm with low blasts diagnosed 2020 (ICD-O code: 9985/3)

Interesting Feature(s)

Germline DDX41 mutation - did this predisposed the patient to developing LPL prior to MDS

Did this cause the prolonged cytopenias during treatment
The myelodysplastic neoplasm was diagnosed after patient completed therapy, thought to be de novo but was patient already at risk and was the chemotherapy another driver to the development of myelodysplasia
Could the DDX41 be contributing to the current Waldenstroms Macroglobulinaemia disease status (partial response instead of complete remission)

EA4HP24-LYWS-12

Fulminant Epstein-Barr virus lymphadenitis due to X-linked lymphoproliferative disease

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Case Description
A 16-year-old male presented with a 7-day history of daily fevers, nausea, vomiting, rash, and cervical lymphadenopathy. A CT of the abdomen showed splenomegaly and laboratory tests revealed pancytopenia (WBC 1.8K, HgB 11.1, platelets 80K, ANC 500), and elevated ferritin (7590 U/mL, normal 137 – 838 U/mL). The patient was transported to our hospital due to concern for hemophagocytic lymphohistiocytosis (HLH) where he was found to have significant elevation of soluble IL-2 receptor (9740 U/ml, normal 7.3 -270.7 ng/mL), ferritin (60,606 ng/ml), CXCL9 (107,584 pg/ml, normal <=647 pg/mL) along with EBV viremia (EBV PCR 496,836 IU/ml). Further laboratory testing revealed severe acute hepatitis with elevated transaminases, cholestasis, and mild prolongation of INR. A lymph node and bone marrow biopsy were performed to rule out lymphoma.
Biopsy Fixation Details
Formalin
Frozen Tissue Available
None
Details of Microscopic Findings
Examination of the tissue sections reveals almost complete effacement of the normal nodal architecture; however, there are focal areas with preserved follicles. There is a proliferation of large, atypical cells intermixed with smaller lymphocytes, histocytes, and plasma cells. Numerous tingible body macrophages are seen, giving a "moth-eaten" appearance. The larger cells vary in size and have irregular nuclei, prominent nucleoli, and a moderate amount of cytoplasm. There are also occasional cells with Reed-Sternberg-like morphology. Occasional mitoses are seen.

Immunophenotype

Immunohistochemistry reveals that the larger cells are predominantly B-cells by CD20 and PAX5. CD3 and CD7 highlight numerous background T-cells with only occasional larger positive cells. The T-cells are predominantly CD8 positive. CD30 is positive in a few scattered immunoblasts and there is no coexpression of CD15. ALK1 is negative. EBV by in situ hybridization (EBER) is positive in a minority of the larger cells and smaller lymphocytes.

By flow cytometry, no monoclonal B-cell population is identified and there are lymphocyte populations consistent with reactive T-cells.

Flow cytometry for SLAM-associated protein (SAP) or X-Linked Inhibitor of Apoptosis (XIAP) reveals no expression of SAP in the T or NK-cells. XIAP expression is normal.

Cytogenetics

None performed on the lymph node. The bone marrow showed normal karyotype and AML FISH panel.

Molecular Studies

T-cell clonality screening by PCR revealed no monoclonal T-cell population.

HLH gene sequencing panel exons 2-4 of the *SH2D1A* gene failed to amplify which suggested a possible intragenic deletion in the *SH2D1A* gene involving exons 2-4. A *PRF1* variant of uncertain significance (c.272C>T) was also identified.

SNP microarray formed on the bone marrow showed a 40.6 kb hemizygous deletion from Xq (Xq25), and a 514.9 kb duplication from 3q(3q25.32->3q25.33). The hemizygous deletion results in the disruption of *SH2D1A*, which is associated with X-linked lymphoproliferative disease.

Proposed Diagnosis

Fulminant Epstein-Barr virus lymphadenitis secondary to X-linked lymphoproliferative disease

Interesting Feature(s)

X-linked lymphoproliferative disease (XLP) is a rapidly evolving, life threating disease that requires expedited diagnosis and treatment due to secondary HLH. The differential diagnosis includes non-Hodgkin and Hodgkin lymphoma, which have different treatments and clinical outcomes, thus rapid and accurate diagnosis is critical. The availability of the SAP flow cytometry assay two days after admission helped guide the differential diagnosis and definitive treatment. This case outlines the work up of XLP in a timely manner at a single institution.

EA4HP24-LYWS-37

Atypical lymphoproliferation of the thyroid due to germline-derived *ATM*-mutation potentially causing a disturbed germinal centre reaction

Dr. Magdalena M. Brune, Prof. Alexandar Tzankov

University Hospital Basel, Institute of Medical Genetics and Pathology, Basel, Switzerland

Case Description

A 64-year-old male patient presented with an enlargement of the left, and seven months later of the right thyroid. Cytologically, the differential diagnosis of a lymphoma was rendered. After excision, histology revealed an unusual follicular lymphoproliferation in the thyroid tissue and was therefore sent to the *Swiss lymphoma pathology reference centre* in Basel as a consultation case. Immunohistochemistry showed a physiological distribution of B- and T-cells without expression of BCL2 in the germinal centres. The accompanying plasma cell were polyclonal and B-cell receptor clonality testing via Multiplex-PCR and DNA-fragment analysis could not detect clonal IGH-rearrangement. Next generation sequencing (NGS) with our customized lymphoma panel did not identify any pathogenic mutation, only a variation of the *ATM* gene [c.4709T>C (p.V1570A)] with a variant allelic frequency (VAF) of 42 %, suggestive of a germline variant. Therefore, the case was diagnosed as an atypical, most likely reactive, follicular thyroiditis. During additional scientific workup of the case, we could confirm our initial suspicion that the identified *ATM* mutation represents a germline variant, since it was detectable in micro dissected surround soft tissues with a roughly 50% VAF. Furthermore, NGS analysis of all B-cell receptor components revealed a clonal, unproductive rearrangement of the IGK-gene with a clonal frequency of 22% in the left and 17% in the right thyroid. Still, criteria for malignancy were not fulfilled, but we suspect the underlying germline-derived *ATM* mutation to have caused a disturbed germinal centre reaction. This could have enabled the non-productive and therefore apoptosis-prone IGK clone to survive negative germinal centre selection and cause the described lymphoproliferation within the thyroid.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

Thyroid tissue with extensive interstitial lympho-follicular hyperplasia with partially atypical configurated germinal centres. Recognizable zonation and tingible body macrophages.

Immunophenotype

Physiological expression of lymphocytic markers: CD20-positive B-cells in the germinal centres with intermingled CD5-positive T-cells. No co-expression of CD5 in B-cells. Negativity for BCL2 in the germinal centres, polyclonal plasma cells and physiological

expression of Ki-67 in the germinal centres. Retained expression of PTEN and ARID1A. No pathological over-expression of H3K27m3.

Cytogenetics

No karyotype available.

Molecular Studies

B-cell receptor clonality testing via NGS:
clonal, unproductive rearrangement of the IG-Kappa gene IGKV2-28 - IGKJ1: MQALQTPRD (ATGCAAGCTCTACAAACTCCTCGGGACG)
NGS Lymphoma Panel:
germline-derived *ATM* mutation [c.4709T>C (p.V1570A) (VAF 42%)
no pathogenic mutations

Proposed Diagnosis

Atypical lymphoproliferation due to disturbed germinal centre reaction caused by an *ATM*-germline variant.

Interesting Feature(s)

This case illustrates the potential consequences of germline variants of critical genes such as *ATM*. Our observations are in line with the known role of certain germline (and somatic) mutations in the development of lymphoproliferations and lymphomas in patients with inborn errors of immunity, such as autoimmune lymphoproliferative syndrome (ALPS), ataxia-teleangiectasia (A-T) and immunodeficiency caused by germline loss-of-function mutations in *STAT3*. Analogously, in our case the *ATM* mutation might have provided fertile ground for the autonomous proliferation of the otherwise apoptosis-prone IGK clone resulting in the described atypical lymphoproliferation within the thyroid.

EA4HP24-LYWS-42

Autoimmune Lymphoproliferative Syndrome

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Case Description

An 8-year-old boy presented with an enlarged, non-tender cervical lymph node. He was treated with Augmentin, but lymph node fluctuated in size without resolution for a year. A CT scan revealed extensive bilateral cervical, axillary, and upper mediastinal lymphadenopathy, and splenomegaly. Despite the absence of fevers, night sweats, or bruising, the patient lost approximately 6 pounds during the course of the disease. Extensive workup ruled out infectious causes. An excisional biopsy of right neck lymph node showed reactive follicular and paracortical lymphoid hyperplasia. The lymphadenopathy continued to wax and wane, prompting a left neck lymph node biopsy (specimen 1) a year later. Both flow cytometry and morphological findings were compatible with autoimmune lymphoproliferative syndrome (ALPS). A diagnosis was further

confirmed by a positive *FAS* gene mutational analysis. Subsequent treatment with sirolimus resulted in a positive response. At the age of 23, the patient presented with right inguinal lymphadenopathy, which was biopsied (specimen 2) and exhibited features consistent with ALPS.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Specimen 1: Marked interfollicular expansion by a mixed population of cells, including small lymphocytes, plasma cells, immunoblasts, and histiocytes.

Specimen 2: Interfollicular expansion by small mature lymphocytes, plasma cells, and scattered epithelioid histiocytes. Follicles had reactive germinal centers.

Immunophenotype

Specimen 1 Flow cytometry: A distinct CD4/CD8 double-negative T (DNT) cell population was detected (15%). Immunostaining identified CD4/CD8 DNT cells in the interfollicular areas.

Specimen 2 Flow cytometry: A distinct polytypic, CD4/CD8 DNT cells was detected (22%). These T-cells coexpressed CD2, CD3, CD5, CD45, and TRBC1 (partial, polytypic pattern), and were negative for CD4, CD8, CD7, and TCR-gamma/delta. These findings were confirmed by immunostaining.

Cytogenetics

N/A

Molecular Studies

A missense mutation, 621 T>C (C127R), in the *FAS* gene was detected by PCR-based sequence analysis in patient and his mother, consistent with ALPS type 1A.

Proposed Diagnosis

Autoimmune lymphoproliferative syndrome (ALPS), type 1A

Interesting Feature(s)

This case represents a rare type 1A, autosomal dominant ALPS with a germline *FAS* gene mutation. Genetic defects in the apoptosis pathway leading to abnormal accumulation of TCRαβ+ CD4/CD8 DNT cells are characteristic of ALPS. Germline variants in *FAS* are the most common cause of ALPS, followed by somatic mutations in *FAS*. ALPS patients typically present in childhood with lymphadenopathy, splenomegaly, and autoimmune cytopenias with an increased susceptibility to lymphomas. The initial diagnosis was missed without flow cytometry and CD4/CD8 immunostaining on the first lymph node biopsy. Flow cytometry with TRBC1 and T-cell markers offers a quick and efficient method to detect polytypic CD4/CD8 DNT cells. A polyclonal T-cell receptor gene rearrangement in ALPS is also helpful to rule out T-cell lymphoma. Lack of awareness of ALPS can result in misdiagnosis as T-cell lymphoma. Conversely, other diseases can present with an ALPS-like phenotype, including other inborn errors of immunity, Evans syndrome, Rosai-Dorfman disease, and nodular lymphocyte-predominant Hodgkin disease. Diagnosis of ALPS necessitates correlation with clinical presentation, family history, in addition to flow cytometry, histology, and genetic testing.

EA4HP24-LYWS-43

•Lymphoproliferative EBV positive disease with morphologic features resembling follicular lymphoma high grade (Grade 3a)

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Case Description

- 27 y/o male patient was diagnosed in early childhood with Wiskott-Aldrich syndrome
- He had numerous repetitive pneumonias, enteritides, eczema and abscesses of the soft tissue
- After the new episode of pneumonia, he presented with generalised lymphadenopathy
- He had also B symptoms (night sweats)
- CT scan showed increased mediastinal, retroperitoneal and peripheral lymph nodes
- A lymph node from the left inguinal region was excised
- Lymphoproliferative EBV+ disease morphologically FL HG (grade 3a) was established.
- Due to immunodeficiency a modified chemo therapy was indicated
- He receivied therapy with specific T lymphocytes (donated by his sister) for EBV infection in combination with Gancyclovir and Rituximab
- The disease evolved with multiorgan failure and the patient died

Biopsy Fixation Details

Formalin fixed (buffered 10%) and paraphine embeded

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph node with nodular architecture. There are well defined nodules composed of mixture of predominantly big centroblasts, which are intermingeled with some smaller centrocytes and FDC. Some bigger follicles are almost completly composed of centroblasts. There is also focal loss of FDC meshworks

Immunophenotype

•Tumor cells are CD20+, bcl6 +, CD 10+, bcl2 -, GCET +, Cyclin D1 -, CD5-. CD23 and CD21 showed remnants of the FDC mashworks. The centroblasts in the bigger nodules are diffusely EBV+. Proliferative marker MIB-1 is very high, especially in the bigger nodules and lower in the surrounding lymphoma cells.

Cytogenetics

FISH t(14;18) negative

Molecular Studies

•PCR showed monoclonal B cell population with IGH and IGK rearrangement

•NGS showed tumor with GCB cell of origin

Proposed Diagnosis

•Lymphoproliferative EBV positive disease with morphologic features resembling follicular lymphoma high grade (Grade 3a)

Interesting Feature(s)

•**Wiskott–Aldrich syndrome** (**WAS**) is a rare X-linked recessive disease characterized by eczema, thrombocytopenia, immune deficiency, and bloody diarrhea (secondary to the thrombocytopenia).

•The WAS-related disorders of X-linked thrombocytopenia (XLT) and X-linked congenital neutropenia (XLN) may present with similar but less severe symptoms and are caused by mutations of the same gene.

•EBV positive lymphoproliferative disease is PTLD like lesion, which may cause fatal outcome in patients with primary immunodeficiency

EA4HP24-LYWS-49

Nodular Lymphocyte Predominant Hodgkin Lymphoma Arising in Autoimmune Lymphoproliferative Syndrome: T cells, Histiocytes and FAS

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Case Description

A 43-year old woman had a childhood history of idiopathic thrombocytopenic purpura, requiring splenectomy, and marked diffuse lymphadenopathy with multiple biopsies showing follicular hyperplasia. She was found to have a *FAS* mutation (c.637 (+1) G>A) and was diagnosed with autoimmune lymphoproliferative syndrome (ALPS). Another member of her family carries the same mutation and diagnosis. At 43 years of age, she presented with increased bulky axillary lymphadenopathy and peripheral blood leukocytosis.

Biopsy Fixation Details

B-plus fixative or formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The axillary lymph node excision was vaguely nodular with complete effacement by a mixed infiltrate predominantly of small lymphocytes and histiocytes, with scattered large atypical lymphoid cells. The large cells had irregular nuclear contours, prominent nucleoli, open chromatin and abundant cytoplasm; their appearance was consistent with lymphocyte-predominant (LP) cells.

Immunophenotype

Flow cytometry showed polytypic B cells and T cells with normal expression of CD2, CD5, CD7 and no gain of CD10. A distinct population of CD4+CD8+ double-positive T cells and a smaller population of CD4- CD8- double-negative non-gamma/delta T cells were present. On immunohistochemical stains, the LP cells were positive for CD20, PAX5, OCT2, BCL6 and negative for CD30 and CD15. In situ hybridization was negative for EBER. The majority of the small lymphocytes were CD3+ CD4+ T cells, with a smaller population of CD8+ CD3+ T cells present. The T cells were CD57+ (subset), CD278/ ICOS+ (weak, subset) with variable PD-1 staining. Assessment for double-positive (CD4+CD8+) T cells and double-negative (CD4-CD8-) T cells was precluded by T-cell density. Small B cells (CD20+ PAX5+ OCT-2+) were a minority of the small lymphocytes. Follicular dendritic cell meshworks were highlighted focally by CD21, CD23 and CD35. S100 stain weakly highlighted histiocytes with a subset showing limited emperipolesis.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) arising in ALPS

Interesting Feature(s)

This case of NLPHL arising in ALPS, by our review, represents the oldest reported woman diagnosed with lymphoma arising in ALPS, a condition with mostly childhood complications. This case showed (1) double negative (CD4-CD8-) non-gamma delta T cells, a finding associated with ALPS, (2) double positive (CD4+CD8+) T cells due to NLPHL, and (3) increased histiocytes with S100 staining and emperipolesis, as previously reported in both ALPS and NLPHL. Also, the altered T-cell populations did not form well-delineated rosettes or stain diffusely for PD-1, as would be expected for NLPHL. Though rare, reported ALPS cases have coincided with diverse hematolymphoid malignancies including a relatively high number of NLPHL and T-cell/histiocyte rich large B-cell lymphomas. Although speculative, NLPHL has molecular changes (such as decreased c-FLIP) that imply that NLPHL may be more susceptible to FAS-mediated apoptosis, raising the possibility of increased survival of NLPHL cells in ALPS, where FAS-mediated apoptosis is prevented. These findings in ALPS suggest that investigation into the role of FAS in NLPHL may inform NLPHL treatment for the general population.

EA4HP24-LYWS-66

Autoimmune lymphoproliferative syndrome (ALPS) with features of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman Disease)

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Case Description

A 5-year-old female of Jamaican descent with no past medical history presented with left cervical adenopathy. Physical exam and radiologic studies revealed adenopathy of a left cervical lymph node measuring 4 cm x 3.5 cm that is oval, nontender to touch, and firm. Her CBC showed mild normocytic anemia explained by beta chain variant Hemoglobin Hope. Immunoglobulin (G, A, M) levels are normal. There is a family history of lymphadenopathy in the patient's mother and two maternal half cousins and a history of recurrent infections in a maternal half aunt.

Biopsy Fixation Details

A lymph node biopsy was fixed in formalin and stained with H&E and immunohistochemical stains per routine protocol.

Frozen Tissue Available

Yes

Details of Microscopic Findings

H&E-stained sections show a markedly enlarged lymph node with prominently thickened fibrous capsule with an expansion of sinusoids by an atypical infiltrate of large histiocytes with prominent nucleoli and emperipolesis. Residual small follicles with secondary germinal centers and intact mantles are also present are present at the periphery. The interfollicular areas were expanded and were comprised small lymphocytes, macrophages, dendritic cells and sclerosis. Within the capsule and interstitial areas were numerous clusters of mature plasma cells.

Immunophenotype

The intrasinusoidal histiocytes are S100+ CD1a-, and Langerin- with emperipolesis of small CD3+ BCL2+ T cells or CD20+ B cells. CD3, CD5, and BCL2 highlight numerous small T cells and CD20 stains scattered B cells in a physiologic distribution. Germinal centers are highlighted by CD10 and BCL6 that are negative for BCL-2. CD138 highlights numerous clusters of plasma cells with a mild kappa bias (kappa to lambda ratio of ~5:1). ALK1 and EBER(ish) are negative. Ki67 shows a proliferative index of 60-70% within germinal centers and 5-10% elsewhere.

Flow cytometric studies showed a population of CD3+ CD4- CD8- (double-negative) T cells accounting for 4% of T cells in a lymph node specimen and 23% of T cells in peripheral blood.

Cytogenetics

None

Molecular Studies

Germline genetics work up including an autoimmune lymphoproliferative syndrome (ALPS) panel (Cincinnati Children's) and a primary immunodeficiency panel (Invitae) did not reveal disease-causing variants.

Proposed Diagnosis

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman Disease) associated with autoimmune lymphoproliferative syndrome (ALPS)

Interesting Feature(s)

The morphology of the lymph node showed thickened fibrous capsule, expanded sinusoids, atypical histiocytes (S100+, CD1a-) and emperipolesis which suggests a diagnosis of RDD. However, the clinical picture combined with the flow cytometry results (double negative T cells) suggests a diagnosis of ALPS. Rare cases of RDD have been reported to be associated with autoimmune disorders such as ALPS. Up to 41% of ALPS patients have features of RDD (Maric, et al. 2005).

EA4HP24-LYWS-75

T-cell large granular lymphocytic leukemia (T-LGLL) in the context of likely somatic*GATA2* mutation

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Case Description

The patient is a 30-year-old female with Turner syndrome, long-standing history of macrocytosis, pancytopenia, splenomegaly, and Evans syndrome (age 12). Of note, the patient has recurrent warts, chronic HPV and a skin BCC. A year before this biopsy, she was diagnosed with T-LGLL and treated with cyclosporine. Due to lack of improvement and worsening macrocytosis, she underwent this bone marrow biopsy. After this biopsy, she was started on methotrexate, with no response.

Biopsy Fixation Details

B-plus

Frozen Tissue Available

No

Details of Microscopic Findings

The bone marrow is hypercellular with moderate reticulin fibrosis, maturing trilineage hematopoiesis, mild eosinophilia, and megakaryocytic atypia. There is no increase in blasts. Interstitial lymphocytosis (CD3+) is seen.

Immunophenotype

Flow cytometry shows relative lymphocytosis (61% of total cells are lymphocytes, of which 95% are CD3+ T-cells). The majority of T-cells are atypical: CD2+, CD8+, loss of CD7 and CD5, partial CD57, CD56-.

Cytogenetics

Karyotype: Failed.

MDS FISH: Normal results for the 5, 7, and 17 probe sets.

Molecular Studies

NGS panel (peripheral blood, not on this biopsy): *GATA2* p.Y314H. While this mutation was classified as a VUS and has not been described before, it is located in the zinc finger region, location of multiple known pathogenic mutations in *GATA2*. However, the VAF was in the 20-28% range over several tests in the year since index biopsy, skin fibroblast testing was negative for the mutation, and parents and sibling are also negative.

TCR gene rearrangement (peripheral blood, not on this biopsy): positive for clonality.

Proposed Diagnosis

T-LGLL in the context of *GATA2* mutation

Interesting Feature(s)

This case features a young adult with T-LGLL resistant to immunosuppressive therapies, longstanding pancytopenia, and hypercellular bone marrow with reticulin fibrosis and megakaryocytic atypia. Interestingly, she was found to have a VUS in the *GATA2* gene. The location and type of mutation raise the possibility of it being pathogenic. Thus, two main scenarios are considered: that she has two independent processes, or that the *GATA2* gene mutation underlies her bone marrow pathologies. Patients with germline *GATA2* deficiency present with disorders of hematopoiesis and/or immunity. These includes findings in our patient of bone marrow hypercellularity, fibrosis and megakaryocytic atypia (can progress to MDS/AML), atypical proliferation of LGL cells, cytopenias, recurrent warts and skin tumors. This scenario is supported by the patient's young age (unusual for T-LGLL) and lack of *STAT* mutations (commonly seen in T-LGLL). However, the low VAF, negative fibroblast testing, and family members negative for mutation argue that the mutation is more likely somatic. In that scenario, the T-LGLL could be due to autoimmunity (of note, Turner Syndrome patients have increased rates of autoimmunity) and is independent of the *GATA2* mutation. Bone marrow hypercellularity, fibrosis and cytopenias could be consequence of both autoimmunity/T-LGLL and *GATA2* mutation, while the latter may also contribute to megakaryocytic atypia (evolving MDS?). Other possibilities to consider include *GATA2* mutation as a somatic CCUS mutation, now with an LGL escape clone. Another is somatic mutation in the setting of longstanding autoimmune disease and increased bone marrow turnover.

In summary, this case highlights the difficulty of understanding the associations of atypical lymphoid proliferations with germline or somatic genetic variants. This can be an important distinction as it informs the decision whether and when to proceed to bone marrow transplant.

EA4HP24-LYWS-108

Sequential T-lymphoblastic lymphoma and diffuse large B-cell lymphoma, NOS, arising in a child with ataxia telangiectasia.

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Case Description

A 1-year-old girl presented with difficulty breathing and swallowing. A chest CT showed a 7.0 cm anterior mediastinal mass compressing the superior vena cava and trachea. A biopsy of the mass revealed a T-lymphoblastic lymphoma/leukemia, and a bone marrow biopsy showed only low-level involvement. She was treated with vincristine, daunorubicin, dexrazoxane, dexamethasone, intrathecal methotrexate, and intrathecal Ara-C, resulting in complete remission. During her chemotherapy, she developed multiple severe infections, leading to assessment for primary immunodeficiency. Genetic testing revealed two pathogenic *ATM* mutations, resulting in a diagnosis of ataxia-telangiectasia. Three years later, she presented with severe back pain. An abdominal ultrasound revealed multiple liver lesions. A liver biopsy demonstrated a diffuse large B-cell lymphoma (DLBCL) with a germinal center phenotype, and a staging bone marrow biopsy was positive.

Biopsy Fixation Details

Formalin, B+

Frozen Tissue Available

Yes (mediastinal mass only)

Details of Microscopic Findings

Mediastinal Mass: The histologic sections revealed sheets of medium-sized lymphoblasts with scant amphophilic cytoplasm and fine chromatin, indistinct nucleoli, and mild nuclear atypia.

Liver: The histologic sections showed cores of liver containing sheets of atypical pleomorphic large lymphoid cells with vesicular chromatin and prominent nucleoli. Apoptotic bodies are frequent and mitotic figures are readily identified.

Immunophenotype

Mediastinal mass: Flow cytometry demonstrated an abnormal T-lymphoblast population, positive for CD45 (dim), CD2, CD5, CD10, cytoplasmic CD3, TdT (strong), CD1a, and CD7 (heterogenous), and negative for CD34, surface CD3, CD4, CD8, CD56, CD16/57, CD19, and MPO. Immunohistochemical stains performed on the mediastinal mass demonstrated diffuse cytoplasmic CD3 expression and patchy, weak TdT staining. CD34 and CD20 stains were negative in the lesional cells. Ki-67 showed a high proliferative index, >80%.

Liver: Immunostains demonstrated diffuse strong expression of CD20, CD19, BCL6, and CD10, with partial expression of BCL2, MYC, and MUM1, and lacked expression of TdT, EBER, CD34, and Cyclin D1. Ki67 showed a high proliferative index, approaching 100%.

Cytogenetics

Conventional karyotyping of the mediastinal mass failed.

Fluorescence in-situ hybridization studies performed on the liver biopsy were negative for BCL2, BCL6, MYC, and IGH rearrangements.

Molecular Studies

Genetic screening for germline mutations identified low-level mosaicism for monosomy X (12%) in addition to two pathogenic mutations in the ATM gene: c.2308G>T; p.Glu770* (premature stop codon) and c.7630-2A>C (splice acceptor variant).

Proposed Diagnosis

Sequential T-lymphoblastic lymphoma/leukemia and diffuse large B-cell lymphoma, NOS, arising in a child with ataxia telangiectasia.

Interesting Feature(s)

Patients with ataxia telangiectasia (AT) are at an increased risk of malignancy and particularly lymphomas, with a cumulative incidence of approximately 10% by 10 years of age and 20% by 15 years, in some studies. The occurrence of multiple lymphomas is an exceedingly rare phenomenon in AT patients, especially at such a young age. This patient had an exceptional clinical trajectory, acquiring both a T-lymphoblastic leukemia/lymphoma and a diffuse large B-cell lymphoma by age 5.

EA4HP24-LYWS-130

Incidental B-lymphoblastic lymphoma in a risk reducing bilateral salpingo-oophorectomy for BRCA1 germline mutation

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Case Description

A 49-year-old female patient with a *BRCA1* germline pathogenic mutation presented for risk-reducing bilateral salpingo-oophorectomy (rrBSO) in November 2022. She had no significant past medical, surgical, or social history. Her family history included male breast cancer occurring in her father at age 50y. She underwent a rrBSO procedure, where an incidental B-lymphoblastic leukemia/lymphoma was detected. Bone marrow biopsy showed no evidence of lymphoproliferative disorder, including with minimal/measurable residual disease (MRD) flow cytometry testing, molecular, and cytogenetic testing. The

patient was treated with hyper-CVAD chemotherapy regimen, and remains disease free one year later.

Biopsy Fixation Details

10% formalin for 12 hours

Frozen Tissue Available

No

Details of Microscopic Findings

Bilateral ovaries showed a diffuse, atypical lymphoid proliferation of monotonous medium sized cells with small amounts of cytoplasm, round nuclei, finely stippled chromatin, and occasional small nucleoli, with occasional mitoses noted and foci of apoptosis seen.

Immunophenotype

The neoplastic cells expressed CD19 (strong), CD20 (minor subset), PAX5 (diffuse), CD79a, Myeloperoxidase, CD10, CD34 (diffuse), TdT (diffuse), MUM1 (variable with subset weakly staining), BCL2, LMO2, FOXP1, while negative for CD3, CD13, CD30, CD33, CD117, CD163, BCL6, C-MYC, P53, and EBER ISH. No follicular dendritic cell meshworks were identified by CD23. Ki67 proliferative index was elevated.

Cytogenetics

FISH analysis detected a loss of the 5' portion of *BCL6* in one locus, indicating a BCL6 gene rearrangement, as well as an *IGH::BCL2* fusion. There was no evidence of MYC rearrangement.

SNP array detected multiple unbalanced genomic aberrations including a loss in segment 1p35.3-p35.1, gain in segment 5pter-q31.3 and 5q31.3-qter, and loss in segment 13q14.13-q14.3.

Molecular Studies

IGH and TCR clonality testing showed clonal rearrangements in *IGH* and *TCR* gamma

ARCHER FusionPlex assay detected *BCL2::IGH* fusion with fusion between genes *BCL2* Exon3 (NM_000633) and *IGH* Exon1 (NR_990001).

A 468 gene mutation panel with matched normal control detected mutations in *TP53, CBL*, and a *FLT1* exon splicing variant, as well as loss of *RB1*, gain of chromosome 5q, and rearrangements in *BTG1, BCL2,* and *XBP1*.

Proposed Diagnosis

B-lymphoblastic leukemia/lymphoma with isolated MPO expression.

Interesting Feature(s)

An incidental B-LBL detected in an rrBSO procedure, which has never been reported in this context. There is also no known connection between *BRCA1/2* germline mutations and B-LBL, though B-LBL has been reported in the context of germline *BRCA* mutations. Furthermore, the mutational findings of a germline *BRCA1* mutation and *TP53* mutation may have played a role in the SNP array findings as well as the unusual *IGH::BCL2* fusion.

EA4HP24-LYWS-162

Monocytoid B cell hyperplasia progressing to nodal marginal zone lymphoma with associatedpolymorphous EBV component in a child with CVID

Dr. Shachar Naor[1], Dr. Lianna Marks[2], **Prof. Dita Gratzinger**[3]

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Case Description

The patient is a 10 year old child with a history of common variable immunodeficiency with immunoglobulin subclass deficiency of IgA, IgG2, and IgG4 with anergy to cocci, TB, and Candida, and progressive lymphadenopathy. Lymph node biopsies are submitted from ages 10, 12 and 14.

Biopsy Fixation Details

The lymph node biopsies were formalin fixed and paraffin-embedded

Frozen Tissue Available

No

Details of Microscopic Findings

The initial biopsy shows absent germinal centers and large clusters of monocytoid B cells.
The second biopsy shows complete architectural effacement by sheets of monocytoid and plasmacytoid B cells and clusters of plasma cells, with rare focal larger cells.
The third biopsy again shows similar findings to the second, now with scattered individual larger cells including rare Hodgkin-like cells throughout.

Immunophenotype

The initial biopsy showed CD20 and CD79a+ monocytoid B cells; lack of follicular dendritic cells on CD21 and CD23 staining; and negative EBV by EBER in situ hybricization. Light chain
staining is polytypic.
The second biopsy shows plasma cell kappa light chain restriction. EBER focally highlights variably sized cells.
The third biopsy shows similar findings with extensive variably sized EBER+ cells.

Cytogenetics

Third biopsy: t(14;19) in all cells examined.

Molecular Studies

First biopsy: PCR for IgH rearrangement oligoclonal
Second biopsy: PCR for IgH rearrangement monoclonal

Proposed Diagnosis

First biopsy: Pseudoparacortical hyperplasia with B cell follicle depletion and monocytoid B cell hyperplasia, EBV negative, in the setting of an inborn error of immunity (CVID)
Second biopsy: Nodal marginal zone lymphoma, EBV focally positive, in the setting of an

inborn error of immunity (CVID)
Third biopsy: Nodal marginal zone lymphoma, EBV positive in polymorphous B cell population, in the setting of an inborn error of immunity (CVID)

Interesting Feature(s)

This case demonstrates the progression of chronic lymphadenopathy in the setting of an inborn error of immunity, from monocytoid B cell hyperplasia through monoclonal B cell lymphoma
with monocytoid morphologic features. There is also acquisition of EBV positivity, at first focal and then extensive, possibly the result of progressive immunosuppression. The relationship of
the polymorphous EBV+ B cell population to the clonal monocytoid lymphoma is unclear, as is the correct classification of the B cell lymphoma. Reports of both EBV+ and, less commonly,
EBV- marginal zone lymphomas in the immunodeficiency setting are rare, largely in the post transplant setting, and largely extranodal rather than nodal (see references).

References:
1. Galera P, Flavin R, Savage NM, Saksena A, Gong S, Wang HY, Swan N, Xi L, Raffeld M, Pittaluga S, Jaffe ES. Epstein-Barr Virus-negative Marginal Zone Lymphoma as an Uncommon Form of
Monomorphic Posttransplant Lymphoproliferative Disorder. Am J Surg Pathol. 2020 Oct;44(10):1340-1352. PMID: 32554995.
2. Gong S, Crane GM, McCall CM, Xiao W, Ganapathi KA, Cuka N, Davies-Hill T, Xi L, Raffeld M, Pittaluga S, Duffield AS, Jaffe ES. Expanding the Spectrum of EBV-positive Marginal Zone
Lymphomas: A Lesion Associated With Diverse Immunodeficiency Settings. Am J Surg Pathol. 2018 Oct;42(10):1306-1316. PMID: 29957733.

EA4HP24-LYWS-166

Atypical plasmacytic and immunoblastic proliferation in a lymph node from a Wiskott-Aldrich patient

Dr. Shachar Naor[1], Dr. Lianna Marks[2], **Prof. Dita Gratzinger**[3]

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Case Description

1.5 yo male with Wiskott-Aldrich syndrome presented with new onset generalized lymphadenopathy and known thrombocytopenia. An axillary lymph node excision biopsy was performed.

Biopsy Fixation Details

The lymph node biopsy was formalin fixed and paraffin-embedded.

Frozen Tissue Available

No

Details of Microscopic Findings

The architecture is preserved but abnormal, showing naked germinal centers and expansion of the paracortical areas by a population of activated large immunoblast-like cells with prominent nucleoli, plasmacytoid cells and plasma cells, with prominent mitotic figures.

Immunophenotype

Flow cytometry shows polytypic B cells, including a CD45+, CD19+, CD38+, CD20+ (dim) population with polytypic light chain expression consistent with polytypic plasma cells/plasmablasts.

CD20 highlights germinal centers with CD21+ follicular dendritic cell meshworks, and scattered cells in the paracortex. CD3 highlights scattered cells in the paracortex. CD138 highlights clusters of plasma cells in the paracortex. EBER EBV in situ hybridization is negative.

Cytogenetics

No

Molecular Studies

No

Proposed Diagnosis

Atypical paracortical hyperplasia with polytypic plasmacytosis and immunoblast proliferation, EBV negative, in the setting of inborn error of immunity (Wiskott-Aldrich)

Interesting Feature(s)

Interesting feature of submitted case:

Paracortical expansion by sheets of atypical plasma cells and B immunoblasts with high mitotic activity, which could raise concern for an aggressive B cell lymphoma, especially on a limited specimen such as a needle core biopsy. A possible mechanism for the abnormal germinal centers and excess plasma cells typical of WAS lymph nodes involves the role of WASp in actin polymerization, which is required for the proper immune synapse formation and antigen engagement between the follicular dendritic cells, follicular helper T cells and the B cells in the germinal center.

References:

1. Snover DC, Frizzera G, Spector BD, Perry GS 3rd, Kersey JH. Wiskott-Aldrich syndrome: histopathologic findings in the lymph nodes and spleens of 15 patients. Hum Pathol. 1981 Sep;12(9):821-31. PMID: 6975749.

2. Zhang X, Dai R, Li W, Zhao H, Zhang Y, Zhou L, Du H, Luo G, Wu J, Niu L, An Y, Zhang Z, Ding Y, Song W, Liu C, Zhao X. Abnormalities of follicular helper T -cell number and function in Wiskott-Aldrich syndrome. Blood. 2016 Jun 23;127(25):3180-91. Erratum in: Blood. 2020 Jun 11;135(24):2198. PMID: 27170596; PMCID: PMC4929975.

3. Descatoire M, Fritzen R, Rotman S, Kuntzelman G, Leber XC, Droz-Georget S, Thrasher AJ, Traggiai E, Candotti F. Critical role of WASp in germinal center tolerance through

regulation of B cell apoptosis and diversification. Cell Rep. 2022 Mar 8;38(10):110474. doi: 10.1016/j.celrep.2022.110474. PMID: 35263577.

EA4HP24-LYWS-177

Inborn Error of Immunity (ITK mutation)-associated Lymphoproliferative Disorder, classic Hodgkin lymphoma, EBV+.

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Case Description

A 20-month-old female presented with cervical lymphadenopathy (LAD) and was diagnosed with classic Hodgkin lymphoma (CHL). She achieved complete remission after therapy, but therapeutic course was complicated by recurrent febrile neutropenia and herpes simplex stomatitis. Over the ensuing years, the patient had multiple infections, including chronic sinusitis, otitis media and pneumonia. At 4.5 years of age, new left cervical and right inguinal LAD was noted with biopsies showing florid follicular hyperplasia. Three months later, biopsy of another left cervical LN revealed CHL. She underwent chemotherapy again and achieved complete remission. Due to her atypical presentation and clinical course, an underlying immunodeficiency was suspected. Immune work up revealed normal serum quantitative immunoglobulins, but low T- (441 cells/uL), B- (216 cells/uL), and NK- (61 cells/uL) cells. Genetic testing was performed, and the patient was found to be a compound heterozygote for mutations in the *IL-2-inducible T-cell kinase* (*ITK*) gene. She underwent an allogeneic stem cell transplant from a sibling donor without evidence of *ITK* mutations and is disease free 12-years post-transplantation.

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

Prior LN biopsies showed CHL and florid follicular hyperplasia.

Sections of the submitted left cervical LN biopsy shows effacement of nodal architecture by an atypical polymorphous infiltrate composed predominantly of small lymphocytes, histiocytes, eosinophils, and scattered large, atypical lymphocytes with Hodgkin (H) and Reed-Sternberg (R-S) morphology.

Immunophenotype

CD45-, CD30+, CD15+, PAX5(weak)+, MUM1+, CD20-, OCT2-, and BCL6-/(weak)+. In situ hybridization for EBER mRNA was positive.

Cytogenetics

G-band karyotype: 48,X,-X,+2,der(10)add(10)(p13)add(10)(q34),del(11)(q22q23),+12,-13,+1~2mar[4]/46,XX[12].

Molecular Studies

Cervical LN biopsy: PCR analysis for *IgH* gene rearrangement demonstrated a clonal product.Genomic DNA from PB was sequenced using primers targeting the entire coding region and exon/intron boundaries of the *ITK* (5q31-q32) and *MagT1* (Xq21.1) genes, revealing two *ITK* mutations: Allele 1: C49T; Allele 2: 922delG.

Proposed Diagnosis

Inborn errors of immunity (IEI)-associated lymphoproliferative disorder, classic Hodgkin lymphoma, mixed cellularity type, EBV+.

Interesting Feature(s)

IEI due to genetic variants can lead to a variety of immune defects in one or more immune cells, predisposing patients to recurrent infections and increasing risk for developing malignancies, including lymphoproliferative disorders (LPDs). Our patient had an unusual, early presentation of CHL, increased infectious complications during and after treatment, and recurrence of CHL. Subsequent genetic testing revealed heterozygous *ITK* mutations encoding truncated and nonfunctional ITK proteins.

ITK is a cytoplasmic receptor tyrosine kinase playing a critical role in antiviral immune responses. Mutations causing *ITK* deficiency result in reduced numbers of CD4+ T-cells and invariant NK-T-cells, failure of CD8+ T-cells to expand/differentiate into CTLs, and diminished CTL cytokine production. *ITK* deficiency is associated with EBV-associated LPDs, including CHL, LBCL, and Burkitt lymphoma. The current case highlights the need for heightened clinical suspicion for IEIs and immune/genetic testing when pediatric patients present with lymphoid malignancies with an atypical clinical course suggestive of an immune dysregulated state. This allows for early adoption of appropriate therapy for disease control and cure.

EA4HP24-LYWS-178

Inborn Error of Immunity (NKD)-associated Lymphoproliferative Disorder, EBV+ with Hodgkin-like Features.

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Case Description

A 30-year-old male with congenital functional NK-cell deficiency (NKD) resulting in severe and recurrent infections throughout life, presented with inguinal lymphadenopathy (LAD). Imaging showed diffuse intraabdominal, pelvic and inguinal LAD and splenomegaly. Inguinal LN biopsy was consistent with an inborn error of immunity (IEI)-associated lymphoproliferative disorder (LPD), EBV+ with Hodgkin-like features. Prior immunodeficiency work-up, included CBC revealing: WBC 6.6, and differential showing neutrophils 53.2%, monocytes 11.4% and lymphocytes 26.3%. Flow cytometry of the PB showed the lymphocyte subsets to be within normal ranges, including total CD3-/CD16+/CD56+ NK cells (17.7% of lymphocytes), CD56(dim)+ mature (10.2%) and CD56(bright)+ immature (1.62%) NK cell subsets. Functional testing of NK cells assessed by a 51Cr-release assay demonstrated cytolytic activity 1 SD lower than healthy individuals. Whole exome sequencing (WES) revealed a de novo G342D beta actin variant. Despite multiple different therapies over one year, repeat lymph node biopsies and imaging studies confirmed progression of disease. The patient succumbed to pneumonia while receiving treatment.

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

Multiple LN samples showed effacement of architecture by polymorphic infiltrates of large, atypical lymphocytes admixed with small and intermediate-sized lymphocytes, many histiocytes, scattered plasma cells and eosinophils. Coagulative necrosis was present. The large, atypical lymphocytes showed a morphologic spectrum, ranging from centroblast-like cells to Hodgkin (H) and Reed-Sternberg (RS) cells, including H-RS variants and mummified cells.

Immunophenotype

CD45+/-, CD30+, CD15+/-, PAX5(weak)+, CD20-, CD79a-, BCL6+/-, MUM1+, PD-L1+, BCL2+/-, EBER ISH+, LMP1+, and EBNA2-.

Cytogenetics

Normal karyotype.

Molecular Studies

Whole exome sequencing revealed a *de novo* novel G342D beta actin variant, later shown to lead to NK cell dysfunction.*IGH* by PCR: clonal gene rearrangement.

Proposed Diagnosis

IEI (NKD)-associated LPD, EBV+, CD30+, with Hodgkin-like features.

Interesting Feature(s)

NKD is a rare type of IEI where a NK cell abnormality is the primary defect causing immunodeficiency. NKD, either through diminished numbers or diminished function of cells, usually results in atypical and severe manifestations of herpesviruses (i.e., EBV) and wart-viruses. Interestingly, despite NK cell importance in cancer surveillance and viral control, the link between NKD and malignancy risk is less well documented than in other IEIs due to the rarity of NKDs.

The differential of EBV+ LPD in our patient includes classic Hodgkin lymphoma (CHL) and a polymorphic B-cell LPD. Extended panels evaluating B-cell antigens and the EBV latency pattern are essential in this setting.

Including our patient, only a handful of case reports have described EBV-driven LPD in NKD patients, including one EBV+ lymphoma and two CHLs. All previously reported cases occurred in pediatric patients, and only one patient had a functional NKD (with cytolytic activity >3SD lower than healthy donors). Older age at presentation of our patient due to relatively better NK function highlights a wider biological spectrum of NKDs, albeit still associated with a heightened risk of developing EBV-driven LPD.

EA4HP24-LYWS-180

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) arising in association with a T-cell rich reactive lymphoid hyperplasia in a patient with activated PI3Kδ syndrome

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Case Description

The patient is a 27-year-old male with a prior history of ileocolic intussusception at age 8 years, splenomegaly and mild thrombocytopenia since 16 years of age, and a benign lymphoepithelial cyst of the left parotid diagnosed at age 22 years. He also has multiple food allergies, eczema, and recurrent ear and respiratory infections. He presented with abdominal pain, constipation and diarrhea, and dysphagia. An EGD revealed an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the duodenum. A transverse colon biopsy also showed atypical lymphoid aggregates with prominent T cells. PET/CT revealed no other sites of disease except for focal uptake in the

rectum. Bone marrow biopsy contained scattered lymphoid aggregates and no overt evidence of lymphoma, although a clonal TRG rearrangement was detected. He received localized radiation therapy to the duodenum. Four months later a 1.5 cm perirectal nodule was noted. A biopsy showed a prominent infiltrate of mixed T cells and no evidence of B-cell lymphoma. A repeat biopsy performed 2 months later showed MALT lymphoma and also a prominent T-cell infiltrate similar to previous biopsies. Germline genetic testing demonstrated a heterozygous mutation in *PIK3CD*, consistent with activated PI3Kδ syndrome (APDS).

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Duodenum, transverse colon, and rectal mass biopsies: Relatively similar dense, diffuse and nodular lymphoid infiltrates in the lamina propria composed of mostly small lymphoid cells, variable plasma cells and occasional eosinophils. Bone marrow biopsy: Mildly hypocellular bone marrow (50%) with scattered lymphoid aggregates composed of small lymphoid cells.

Immunophenotype

Duodenum, transverse colon, and rectal mass biopsies: B cells positive for CD20 and CD79a, negative for CD5, CD10, BCL6, CD43, cyclin D1 and SOX11. Plasma cells are lambda restricted in duodenum, are polytypic in the transverse colon and 1st rectal mass biopsy, and IgG kappa restricted in the 2nd rectal mass biopsy. T cells are mixed CD4+ and CD8+, predominantly Beta F1+, show no loss of CD2, CD3, CD5 or CD7, and are negative for CD30, CD56 and TdT. EBV ISH (EBER) and HHV8 is negative. Bone marrow biopsy: Lymphoid aggregates contain mixed CD4+ and CD8+ T cells and few CD20+ B cells. Flow cytometry shows no evidence of a monotypic B-cell or aberrant T-cell population. EBV ISH (EBER) is negative.

Cytogenetics

Bone marrow biopsy: 46,XY[20]

Molecular Studies

1st duodenum biopsy: Clonal IGH rearrangement.

1st transverse colon polypectomy: No clonal IG or TR rearrangements.

Bone marrow biopsy: No clonal IGH rearrangement. Clonal TRG rearrangement; no clonal TRB rearrangement.

1st rectal mass biopsy: Clonal TRG rearrangement; no clonal TRB rearrangement.

2nd rectal mass biopsy: Clonal IG and TR rearrangements.

Germline genetic testing: *PIK3CD* c.3061G>A (p.Glu1021Lys) heterozygous

Proposed Diagnosis

MALT lymphoma arising in association with a T-cell rich reactive lymphoid hyperplasia in a patient with activated PI3Kδ syndrome.

Interesting Feature(s)

This represents a lymphoma arising in a patient with a rare inborn error of immunity, activated PI3Kδ syndrome (APDS). Most lymphomas arising in APDS patients are DLBCLs or CHLs associated with EBV infection, but this patient developed 2 EBV-negative MALT

lymphomas and had no evidence of EBV viremia. Individuals with APDS may exhibit prominent lymphoid hyperplasia in the gastrointestinal tract. There is a potential pitfall of diagnosing a T-cell lymphoma when a clonal TR rearrangement is identified in such patients.

EA4HP24-LYWS-184

Atypical lymphoproliferation and massive fatal hemophagocytosis in an EBV-positive patient with homozygous mutation in the RAB27A

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Case Description

A 21 year male patient with no past medical history, some dysmorphic features, presented with weight loss, headache, abdominal pain, lymphadenopathy and hepatosplenomegaly. The patient had psychotic behaviour, MRI brain showed demyelinating lesion. EBV PCR was positive(6281IU/mL). Peripheral blood shows pancytopenia of severe degree. The first bone marrow showed atypical lymphoid infiltrate with inconclusive diagnosis. A repeat BM (4 months later) revealed evident hemophagocytosis, at that time the patient had fever, high ferritin (2,485.0 mcg/L), markedly elevated liver functions, hypofibrinogenemia (0.39 gm/L). HLH was diagnosed and treatment started with no response and the patient passed away, four months after diagnosis.

Biopsy Fixation Details

AZF fixed

Frozen Tissue Available

N/A

Details of Microscopic Findings

BM aspirate smear shows trilineage hematopoiesis with increased lymphocytes (31%), mature-looking. Histiocytes/macrophages are prominent with evident erythrophagocytic activity.The BM biopsy is hypercellular and extensively infiltrated with numerous histiocytes/macrophages exhibiting massive erythrophagocytic activity. There are multiple atypical pleomorphic cellular infiltrates with rather vague nodular pattern composed predominantly of small lymphocytes (mostly T-cells mixed with few B-cells, histiocytes/macrophages, few plasma cells and eosinophils). Residing within the infiltrate

are scattered medium to large mononuclear cellswith prominent nucleoli and/or irregular nuclear contours.

Immunophenotype

Flow cytometry on BM aspirate shows 33% T-cells & 1% B-cells with no definitive immunophenotypic evidence of monotypic B-cell population.

IHC: Some of the mononuclear cells are positive for CD30. CD163/CD68 highlighted marked proliferation of activated macrophages with extensive erythrophagocytosis. EBER by ISH: Negative

Cytogenetics

Normal karyotype

Molecular Studies

Exome sequence analysis revealedHomozygous mutation in the *RAB27A,* c.244C>T, p.R82C.

Proposed Diagnosis

Primary HLH associated with atypical EBV-related lymphoproliferation in a patient with homozygous mutation in the *RAB27A (*Griscelli (type 2)).

Interesting Feature(s)

The diagnosis of this case was challenging and delayed due to non-specific clinical and bone marrow findings with atypical lymphoproliferation. EBV-related lymphoproliferation could not be excluded. Second BM showed the same pattern of florid T-cell infiltrate. However; associated with fulminant erythrophagocytic activity. Our patient satisfied the diagnostic criteria for HLH with (fever, splenomegaly, cytopenia, hypofibrinoginemia, hyperferritinemia, hemophagocytosis).

RAB27A encodes a GTP binding protein in RAS-superfamily, biallelic pathogenic variants in *RAB27A* are associated with Griscelli syndrome subtype 2(GS2), a rare autosomal recessive disorder, primarily associated with immunological dysfunction and the development of hemophagocytic lymphohistiocytosis (HLH). Primary HLH are usually diagnosed in infancy and rarely present at later age as in our case.

Primary HLH results from homozygous mutations in NK & CD8 T cell cytolytic pathway genes. *RAB27A* mutation is associated with decreased NK cytolytic activity, and it has been reported that defective perforin-mediated cell lysis by NK cells & CD8 T cells results in prolonged interaction between the cytolytic cell & the antigen presenting cell, and thus contributes to a pro-inflammatory cytokine storm responsible for the clinical features associated with HLH.

EA4HP24-LYWS-200

Relapsed classic Hodgkin lymphoma; when to suspect an underlying inborn error of immunity

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Case Description

A 23 year old male patient presented with weight loss and night sweats. A mediastinal mass, bilateral cervical and supraclavicular lymphadenopathy and small upper abdominal lymph nodes were noted. A cervical lymph node biopsy was performed and a diagnosis of classic Hodgkin lymphoma (CHL), EBV-negative was made. The patient was treated with 6x BEACOPP and reached complete remission. He presented with relapsed disease with supradiaphragmatic involvement 46 months later. A lymph node biopsy was interpreted as CHL, EBV-positive. He received high-dose chemotherapy and autologous bone marrow stem cell transplant (SCT). Subsequently, he developed steroid-refractory auto-immune thrombocytopenia and additionally based on a medical history of bronchiectasis, an immunological evaluation and NGS-work-up for inborn error of immunity (IEI) was initiated. Pathogenetic (class PVS1) , loss-of-function germline mutation in magnesium transporter 1 (*MAGT1*) was diagnosed, consistent with the rare X-linked IEI XMEN. The diagnosis was confirmed by decreased NKG2D expression on CD8-positive T-cells.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

no

Details of Microscopic Findings

First presentation: Lymphoid tissue with a destructive infiltrate of small lymphocytes, histiocytes, few eosinophils and a sparse component of multinuclear and mononuclear Hodgkin-Reed Sternberg (HRS) cells. No remarkable immunoblastic component.

Relapse: as above. A larger morphological range of HRS-like cells and immunoblasts is noted as was a larger component of plasmacytoid and (polytypic) plasma cells.

Immunophenotype

First presentation: HRS cells positive for CD30, PAX5 (weak), OCT2, CD15 (partly); negative for CD20, CD79a, CD3, GranzymeB, ALK1, EBER, LMP1

Background infiltrate: mixed small B- and T-lymphocytic; sporadic EBER-positive small lymphoid cells

Relapse: HRS-like cells positive for CD30, PAX5 (weak), EBER, CD79a (partly, weak); negative for CD20, CD3, CD15.

Background infiltrate: large component of EBER-positive mononuclear lymphoid cells with a striking morphological range from larger immunoblasts to small lymphocytes

Cytogenetics

no

Molecular Studies

Germline NM_0013679161(MAGT1):.41delp.(Pro137Glnfs_44)

Proposed Diagnosis

First presentation: classic Hodgkin lymphoma, EBV-negative, IEI-setting (XMEN)

Relapse: polymorphic B-lymphoproliferative disorder EBV-positive, IEI-setting (XMEN)

Interesting Feature(s)

At presentation, there were no clinical, cytomorphological or immunophenotypic clues suggestive of an underlying IEI and no arguments against a diagnosis of "common" CHL. At relapse, however, the unusual large morphological spectrum of mono- and multinuclear HRS-like cells, EBER-positivity in both HRS-like cells and in a large range of background lymphoid cells and some immunophenotypical peculiarities deviating from a diagnosis of CHL should alert for an immunodeficiency/dysregulation state, either IEI or post-poly-chemotherapy. Only much later after the diagnosis of XMEN, all pieces of information, and additional ones (e.g. maternal brother died at age 2 of acute leukemia), fell into place. In hindsight, the relapse presentation should rather have been interpreted as polymorphic B-LPD, a known mimicker of CHL. This interpretation would probably have impacted on treatment choices. Currently, the patient and his treating team are considering pre-emptive allogeneic SCT. The case highlights the problem of unrecognized underlying IEI in (young) adult patients and provides opportunity to discuss key features to support timely recognition.

EA4HP24-LYWS-207

Kabuki syndrome induced common variable immunodeficiency (CVID)

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Case Description

A 22 year old male patient, diagnosed with CHARGE syndrome (coloboma of eye, heart defects, atresia of choanae, restriction of growth, ear abnormalities) in childhood but with no chromosomal abnormalities on testing, presented with autoimmune haemolytic anaemia & neutropenia, and was treated with rituximab. He later developed immune

thrombocytopenia. Following episodes of respiratory infections, pan-hypogammaglobulinaemia (IgG < 2 g/L) was noted and common variable immunodeficiency (CVID) was diagnosed. He required regular immunoglobulin replacement. Further investigations detected heterozygous variant for KMT2D. Because of the small volume generalised lymphadenopathy and mild splenomegaly, a needle biopsy of PET positive cervical lymph node was performed (submitted sample).

Biopsy Fixation Details

10% formaldehyde

Frozen Tissue Available

No

Details of Microscopic Findings

Retained normal architecture with reactive follicles showing thin/absent mantle zones. Mild paracortical expansion with occasional eosinophils & neutrophils, only very scant plasma cells & with a single very ill formed microgranuloma.

Immunophenotype

CD20, CD79a, Pax 5: Normal localisation of B cells
CD10, BCL 6, BCL2, Ki67: Reactive germinal centres
IgD: Largely deficient mantle zones
CD138, kappa, lambda: Very scant polytypic plasma cells
CD2, CD3, CD5, CD7: No T-cell antigen loss
CD4, CD8: No double negativity/positivity
EBER, EBV LMP1: -ve
ALK: -ve
CD30, CD15, Pax 5, Mum1: No HRS cells

Cytogenetics

Not performed

Molecular Studies

Genomic analysis using EuroClonality-NDC demonstrated polyclonal B & T cell rearrangements and a pathogenic KMT2D variant c.14713C>T p.(Gln4905Ter) at ~50% allele frequency.

Proposed Diagnosis

Kabuki syndrome induced CVID associated reactive lymphoid hyperplasia

Interesting Feature(s)

CVID is caused by a variety of different genetic abnormalities. Only a few of the defects have been identified with the cause of most cases being unknown. Kabuki syndrome, first described in 1981 is rare (~1 in 13,000 births). Patients show facial resemblance to stage makeup used in Kabuki, a Japanese traditional theatrical form. Type 1 (the majority with autosomal dominant pattern inheritance) is caused by germline heterozygous loss of function variants of KMT2D. Type 2 (with X-linked dominant pattern inheritance) is caused by germline hemizygous (in males) or heterozygous (in females) chromosome deletions or loss of function point variants in KDM6A located on X chromosome. Most cases occur de novo with mutation occurring early in embryonic development but inherited mutations have been reported. Some have no identifiable (so far not detected) mutation. CHARGE syndrome (which the patient was thought to have originally) is clinically distinct but shows

significant phenotypic overlap with Kabuki syndrome. A recent study of gene specific DNA methylation signatures identified epigenetic mechanisms linking these 2 syndromes and this could account for some clinical overlap.
KMT2D, a chromatin modifier, plays a role in perinatal secondary lymphoid tissue development, post activation lymphocyte trafficking & plasmablast terminal differentiation. KMT2D altered mice showed deleterious B-cell differentiation. KMT2D mutation is recurrent in DLBCL & follicular lymphoma (likely an early event). Lymph node pathology of CVID has been well described, but lymph node histo- & molecular pathology in Kabuki syndrome, has not been described. Demonstration of KMT2D variant (43% VAF) without any other molecular genetics abnormality in the lymph node confirms that isolated KMT2D mutation can induce CVID and is responsible for lymph node pathology.

EA4HP24-LYWS-214

Recurrent florid marginal zone hyperplasia

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Case Description
The patient is an 8-year-old girl who presented with right cervical adenopathy and asymmetric tonsillar enlargement, present for about two months. She had normal CBC indices and no history of recent/recurrent infection. Tonsillectomy revealed an atypical marginal zone B-cell proliferation with lambda light chain excess, but without evidence of clonality by gene rearrangement testing. Over the next year, the patient's cervical lymphadenopathy increased. She underwent cervical lymph node excision, revealing similar findings to those of the tonsillectomy although without definitive lambda excess. Six months later, the patient's right cervical adenopathy had recurred and a repeat excision was performed, again showing marginal zone hyperplasia; since this resection, her symptoms have not recurred.
Biopsy Fixation Details
Tissue was sent fresh for flow cytometry and karyotype, and sections were preserved in B-plus for histology.
Frozen Tissue Available
No
Details of Microscopic Findings
Similar morphologic findings were seen in all specimens: distortion of the tonsillar/nodal architecture by a proliferation of expanded follicles, some with attenuated or fragmented germinal centers, with indistinct mantle zones and an expanded perifollicular infiltrate of medium-sized lymphoid cells with round nuclei and moderately abundant pale cytoplasm. The lymph nodes exhibited thickened capsules and bands of sclerosis.

Immunophenotype

By immunohistochemistry, the marginal zone cells were positive for CD20, PAX5, and IgD, and negative for CD43, BCL2, and BCL6. CD21+ follicular dendritic cell meshworks appeared expanded. The germinal centers were BCL6+ and BCL2-, and some contained increased PD1+ T cells. κ and λ light chain staining showed λ-excess in the tonsil but polytypic staining in both lymph nodes. CMV and EBV were negative. Flow cytometry revealed an abundance of CD5-, CD10- B cells; the tonsil showed a decreased κ:λ ratio of 0.6 while both cervical nodes showed a normal κ:λ ratio.

Cytogenetics

Normal female karyotype (second lymph node)

Molecular Studies

IGH gene rearrangement testing was negative on the tonsil and first lymph node. A 447-gene NGS panel on the second lymph node showed no clinically significant SNVs or indels. Whole exome sequencing on the second lymph node did not reveal any significant germline or somatic variants, including in *PIK3CD*.

Proposed Diagnosis

Florid marginal zone hyperplasia

Interesting Feature(s)

The differential diagnosis for this case included pediatric nodal marginal zone lymphoma, atypical marginal zone hyperplasia, marginal zone hyperplasia due todue to activated PI3Kδ syndrome, or a florid reactive process. While the histomorphologic findings and the lambda excess in the tonsillectomy specimen could be consistent with PNMZL, the lack of monoclonal IGH rearrangement and aberrant CD43 expression are against this diagnosis. The activated PI3Kδ syndrome has been associated with polyclonal marginal zone expansion and increased germinal center PD1+ T cells, but the patient did not have recurrent infections or a pathogenic *PIK3CD* variant. Atypical marginal zone hyperplasia can also show light chain restriction, but typically occurs in extranodal sites such as the tonsils and GI tract. Marginal zone hyperplasia of cervical nodes can occur in the setting of *H. influenzae* infection, with recurrent cases previously reported; this is a consideration although patient's infection status is unknown. Overall, while this case was ultimately determined to represent a reactive rather than neoplastic process, its diagnosis was challenging, requiring multiple specimens and extensive ancillary testing.

EA4HP24-LYWS-222

A 64 year old male presenting with autoimmune hemolytic anemia and lymphadenopathy progressing to large B-cell lymphoma over a period of 2.5 years with a germline mutation in PIK3R1.

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Case Description

A 64-year-old male with a history of seminoma at the age of 47, treated with chemotherapy; prostate carcinoma at the age of 59, treated with radical radiation.

At the age of 61 he developed autoimmune hemolytic anemia, splenomegaly and increasing lymphadenopathy. After 1,5 years the anemia worsened, and he received prednisolone. PET CT showed bilateral supraclavicular, axillary, and inguinal lymph nodes as well as mediastinal and right hilar lymph nodes. CHOP treatment was started on suspicion of lymphoma (after second biopsy) with subsequent decrease in lymph node size during treatment.

The patient was biopsied on three occasions (lymph node excisions) over a period of 2.5 years with a progression of histological alterations.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The first lymph node showed mostly preserved structure with paracortical hyperplasia, follicular hyperplasia and monocytoid B-cell hyperplasia around sinuses. There were no overt signs of lymphoma.

1.5 years later an axillary lymph node was excised. The structure was almost completely obliterated with absence of follicles, marked paracortical expansion with lymphoid cells of varying size, some showing immunoblastic features with vesicular nuclei and distinct nucleoli. Some of the larger cells had similarities of HRS-cells, but typical ones were not present. These cells were admixed in a background of small lymphocytes and histiocytes as well as hyperplastic vessels.

The patient received 5 CHOP + 4 rituximab treatments with almost total regression of lymph nodes and considerable reduction of spleen size. Eight months later he relapsed with lymph node enlargement and hemolytic anemia. The lymph node biopsy showed progression of the histologic features with increasing amounts of large B-cells, also in

small clusters, some of them resembling HRS-cells. The histology and immunophenotype was now consistent with a T-cell-rich large B-cell lymphoma.

Immunophenotype

Secon biopsy: The large, scattered cells were B-cells positive for CD30, CD20, CD79, CD19, Pax5, Oct2, MUM1, BOB1 and CD45. These cells were EBER and CD15 negative (a few scattered EBER-positive cells were present). CD21 and CD23 demonstrated numerous small meshwork of follicular dendritic cells with remnants of small B-cells. The dominating population were small T-cells. Many of them CD4 and PD1-positive, some CD8-positive.

Cytogenetics

No

Molecular Studies

Clonality studies showed polyclonal rearrangements of TCR and IgH genes.

NGS: TruSight Oncology 500 Gene Panel demonstrated a splicing factor variant mutation in PIK3R1 (c.1425+1G>T) with VAF of 46%. The same mutation was detected in a bone marrow trephine biopsy (VAF 43%) without lymphoma involvement confirming this was a germline mutation.

Proposed Diagnosis

Atypical paracortical B-cell proliferation, consistent with a B-cell lymphoma, not further classified, associated with activated PIK3D-syndrome 2 (APSD2) with a germline point mutation in PIK3R1 (c.1425+1G>T).

Interesting Feature(s)

This case demonstrates the morphologic evolution in lymph nodes in a patient with a splicing site mutation in the PIK3R1 gene at c.1425+1G>T. This mutation has been reported to result in skipping of exon 11 interfering with the inhibitory effect on PI3K delta leading to activation of downstream PI3K signaling. This patient was older than most previously reported cases. The initial finding was autoimmune hemolytic anemia and over approximately 2.5 years three excised lymph nodes at different time points demonstrated the evolution from reactive hyperplasia to overt large B-cell lymphoma.

EA4HP24-LYWS-231

Spectrum of Atypical lymphoid proliferations in a Patient with Activated Phosphoinositide 3-Kinase δ Syndrome 2

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Case Description

A 7-year-old-girl with Activated PI3K Delta Syndrome 2 (APDS 2), presented with failure to thrive, enlarged tonsils/ adenoids, a right upper quadrant palpable mass, splenomegaly and FDG avid lymph nodes in the bilateral neck, chest, and abdomen.

Biopsy Fixation Details

Formalin Fixed

Frozen Tissue Available

Yes

Details of Microscopic Findings

Part 1 (cervical lymph node) showed T-cell proliferation as well as aggregates of monocytoid B cells, and scattered EBER positive cells. Parts 2 (abdominal lymph node) and 3 (mass on duodenum) showed poorly defined follicles with expansion of follicular dendritic cell meshworks (on CD21) associated with T-follicular helper cell (TFH) proliferation (on CXCL13, CD10, BCL6 and PD1). Part 3 had features similar to part 2 and in addition, there were focal areas with kappa light chain predominance. Ancillary flow cytometry showed no definitive evidence of lymphoma on all three parts.

Immunophenotype

See above

Cytogenetics

Not done

Molecular Studies

- Genetics: Whole exome sequencing identified a *PIK3R1* gene mutation (c.1425+1G>A).
- Clonality assays (B & T) performed on part 1 and part 2 were negative. However, clonality studies on part 3 demonstrated presence of a B-cell clone.

Proposed Diagnosis

The combined morphologic, immunophenotypic and ancillary features show a spectrum of atypical, likely reactive, lymphoid proliferation in the setting of Activated PI3Kδ syndrome 2.

Interesting Feature(s)

APDS2, a combined immunodeficiency is characterized by frequent infections, lymphoproliferation and autoimmunity and carries an increased risk for lymphoma.[1]

This case highlights the spectrum of histopathologic findings in a patient with APDS 2, who presented with chronic cervical lymphadenopathy and a more recent generalized

lymphadenopathy, clinically mimicking lymphoma. We observed varied histomorphology between the various biopsied sites. It showed several features that favored benign lymphoproliferation i.e., atypical follicular hyperplasia, attenuated mantle zones and parasinusoidal aggregates of monocytoid B cells on cervical lymph node biopsy. Whereas, the abdominal lymph node and mass revealed poorly defined follicles, increased immunoblasts, and an atypical expansion of PD1+ T-cells which raised the possibility of a T-cell lymphoma with a TFH-cell phenotype. In addition, the abdominal mass demonstrated focally increased number of plasma cells with an increased kappa/lambda ratio (on in-situ hybridization studies) and a positive B-cell clonality. The T-cell clonality study was negative. This case shows features that have been described in cases with APDS [1-2], but in addition, demonstrates borderline features between reactive proliferations and frank neoplasia which necessitates clinicopathologic correlation.

It underscores the challenges in definitively classifying this immunodeficiency-related lymphoproliferation, which lies on a spectrum of lymphoid hyperplasia and lymphoproliferative disorder and may represent an evolving lymphoproliferative disorder. Hence a close clinical and radiologic follow-up was recommended.

Patient is on immunoglobulin replacement, antibiotic prophylaxis, and currently considered for enrollment in trial for selective PI3Kδ inhibitors Leniolisib. A repeat abdominal ultrasound revealed an interval increase in size of lymph nodes but no subsequent biopsies were taken.

References.

1. J Allergy Clin Immunol. 2016 Jul;138(1):210-218.

2.J Allergy Clin Immunol. 2017 Feb;139(2):597-606.

EA4HP24-LYWS-284

Incidental XLP discovery leading to Burkitt-like lymphoma in a 10-year-old male

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Case Description

A 10-year-old male with a history of anxiety, anger outbursts, and difficulty in school was sent to a psychologist who requested genetic testing. Two regional deletions encompassing 15q11.12 and Xq25, as well as a deletion of a SH2D1A were found, consistent with X-linked lymphoproliferative disease (XLP). A month after this discovery, the patient developed left cervical lymphadenopathy. Due to the predisposition of lymphoma and worsening lymphadenopathy, a lymph node biopsy was performed.

Biopsy Fixation Details

A lymph node from the left neck was received fresh and a portion was fixed in formalin.

Frozen Tissue Available

Frozen tissue is available.

Details of Microscopic Findings

H&E-stained sections show effaced lymph node architecture. There is a diffuse infiltrate composed of mononuclear cells that are small to medium in size and have distinct cytoplasmic borders. Numerous tingible body macrophages are identified. The lymphocytes and macrophages impart a starry-sky pattern to the node. Mitoses are numerous. The Wright-Giemsa stained slides of the touch preparation show variably sized lymphoid cells with deep basophilic cytoplasm that contain vacuoles.

Immunophenotype

Immunohistochemical stains performed with adequate controls display tumor cells that are CD10+, CD20+, BCL6+, BCL2(dim-subset)+, MUM1(subset)+ B-cells. C-MYC is variably positive in ~50-60% of the neoplastic cells. CD3 highlights scattered T cells. CD30, CD34, and TDT are negative. Ki67 proliferation index is >90%. EBER(ISH) is negative. Flow cytometry revealed a SAP deficiency.

Cytogenetics

FISH positive signals for a KMT2A probe

Negative signals for CEP8, MYC, IGH and ETV6, RUNX1 probes.

Molecular Studies

High resolution SNP array of lymph node:

Confirm constitutional deletions

Gains/losses of 11q

Gains long arm chromosome 1 (1q)

Proposed Diagnosis

Burkitt-like lymphoma with 11q aberration (WHO), Large B cell lymphoma with 11q aberration (ICC).

Interesting Feature(s)

Interestingly, this patient did not present with the classic symptoms of XLP, but behavioral issues that prompted genetic studies, where the SH2D1A deletion was found incidentally. X-linked lymphoproliferative disease is a rare immunodeficiency due to deletions of SH2D1A/SAP which results in severe immune dysregulation. Clinical manifestations of this disease are lymphoma, hemophagocytic lymphohistiocytosis (HLH), and reduction of gamma globulins often triggered by Epstein Barr Virus (EBV) infections. Shortly after detection of XLP, Burkitt-like lymphoma with 11q aberration was diagnosed. XLP patients have an increased risk of developing B-cell lymphomas, often EBV+. Interestingly, this patient's lymphoma was not positive for EBV despite being immunodeficient. Burkitt-like lymphoma with 11q aberration (WHO) shares morphologic and immunophenotypic features and a gene expression profile like Burkitt lymphoma but lacks the MYC rearrangement and carries an 11q aberration with proximal gains and telomeric losses. This lymphoma is usually in the head and neck, can show pleomorphic morphology and be associated with a complex karyotype. It is not associated with EBV infection.

EA4HP24-LYWS-285

EBV positive lymphoma and chronic EBV infection in a patient with ataxia telangiectasia

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Case Description

A 6-year-old female with a history of ataxia telangiectasia (AT), prematurity, failure to thrive, and granulomatous skin lesions presents to the emergency room with fever and hepatomegaly. The patient was admitted to the PICU for fluid resuscitation. The patient improved but had sustained elevated liver enzymes and chronically elevated EBV viral load. Given the history of AT, an MRI of the liver was performed and revealed multiple round, solid lesions throughout the liver. Core biopsies of the liver and a bone marrow aspirate and core biopsy were performed.

Biopsy Fixation Details

A core liver biopsy was received fresh. It was submitted for EM, a fragment was kept frozen, and the rest was submitted.

Frozen Tissue Available

Frozen tissue was submitted for genetic testing.

Details of Microscopic Findings

H&E sections core biopsies from the liver lesions show a lymphohistiocytic infiltrate that replaces the normal liver parenchyma. The infiltrate is composed of histiocytes, medium to large sized lymphoid cells with vesicular chromatin, ample amounts of pale eosinophilic cytoplasm and scattered large multinucleated cells with irregular nuclei, some reminiscent of Reed-Sternberg morphology. A bone marrow aspiration and a biopsy revealed a hypercellular bone marrow with trilineage hematopoiesis.

Immunophenotype

Immunohistochemistry performed on paraffin sections of the core biopsy demonstrates most of the atypical population to be CD45 (subset) +, while many of the larger cells are CD45 -. The medium to large size atypical population are CD19 (subset dim)+, CD20 (subset dim) +, CD30 +, MUM1 +, PAX5 +, OCT2 +, BOB1 (subset) +, BCL2 +, EBER (ISH) +, BCL6 (subset) +, CD10 -, CD15 -. CD79a is mostly negative in this population. Small mature CD3 + cells are identified, while the CD4:CD8 ratio is difficult to assess due to the amount of CD4 + histiocytes available. ALK1 is negative.

Cytogenetics

N/A

Molecular Studies

Next generation sequencing (NGS) of the frozen core liver biopsy showed: JAK2 amplification, ABL1 variant (NM_007313.2), c.1475G>A (p.R492Q) and three likely benign variants (FLT3, PIK3R1, and SETD2).

Proposed Diagnosis

Diffuse large B cell lymphoma (EBV+) associated with primary immune disorder (ataxia telangiectasia) (WHO), EBV positive diffuse large B cell lymphoma associated with ataxia telangiectasia (ICC).

Interesting Feature(s)

Ataxia telangiectasia is a rare auto-recessive disorder caused by mutations in the ATM gene, which is involved in repair of double-strand DNA breaks. AT is characterized by cerebellar ataxia, telangiectasias, primary immunodeficiency, and increased incidence of cancers, particularly EBV-associated lymphomas. EBV is an oncogenic virus that establishes a latent infection in B-cells. Immunodeficient patients may have difficulty controlling chronic EBV infection leading to EBV-driven malignancies. Patients with AT are at increased risk of developing EBV-related B cell lymphomas. This patient developed a diffuse large B cell lymphoma, EBV+, associated with primary immunodeficiency, ataxia telangiectasia. The patient was successfully treated for DLBCL. However, she continued to have a high EBV viral load, consistent with chronic EBV. At an outside hospital she received EBV-specific T-cell therapy and died of infection related complications.

EA4HP24-LYWS-288

Mutation in the perforin gene inducing a macrophage activation syndrome

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Case Description

A 17-year-old female patient treated two months previously with Amoxicillin for streptococcal angina, presenting with persistent fever. The workup revealed bi-cytopenia (leukopenia (PNN 1,32 G/L) and thrombocytopenia (platelets 71 G/L)), hyperferritinemia (824µg/L), and hypertriglyceridemia (4.41 mmol/L), associated with hepatosplenomegaly, suggestive of macrophagic activation syndrome (MAS). An exhaustive infectious workup, including serology and PCR, was negative. The diagnosis of lymphoma was suspected and led to a bone marrow workup.

Biopsy Fixation Details

Neutral buffered formalin and EDTA decalcification

Frozen Tissue Available

No

Details of Microscopic Findings

Bone marrow smears showed normal hematopoïsis with reactional lymphoid cells and several macrophages engulfing red blood cells, platelets, and neutrophils.

The bone marrow biopsy was of good size (20 mm). Cellularity was markedly increased for age (100%). Megakaryocytes were of normal shape and size, with no abnormal lobulation. The erythroblastic and granular lineages showed no significant histological abnormalities. There was a dense lymphohistiocytic infiltrate composed of small lymphocytes with regularly outlined hyperchromatic nuclei that were not atypical. They were associated with numerous histiocytes and macrophages with images of hemophagocytosis in favor of MAS. Special stains (PAS, GRAM, Ziehl, Grocott) were negative. An interstitial lymphoid infiltrate was visible on standard staining.

Immunophenotype

The lymphocyte infiltrate was composed of 90% CD3+ T lymphocytes. CD20+ B lymphocytes were scarce. T-cells were 60% CD4 and 40% CD8, with no loss of CD2, CD5 or CD7 expression. Several cells were labeled by granzyme B, but none by perforin. In situ hybridization for EBER RNA was negative.

Cytogenetics

No

Molecular Studies

A study of lymphocyte clonality was performed by PCR (BIOMED-2) but was not contributive due to DNA degradation (100 bp).

Given the absence of perforin expression, the diagnosis of familiar lymphohistiocytosis by perforin mutation was suspected.

Sequencing of the perforin gene identified two heterozygous mutations: p.P39H and p.L441H.

Proposed Diagnosis Primary MAS due to familial hemophagocytic lymphohistiocytosis.

The patient benefited from a haploidentical allogeneic marrow stem-cell transplantation and is in good general condition.

Interesting Feature(s)

This case provides a reminder of the various causes of secondary MAS that the pathologist must investigate.

It highlights a simple tool for raising the hypothesis of familial lymphohistiocytosis. fHLH is indeed an autosomal recessive disorder, characterized by diminished NK cell function and caused by mutations in the perforin gene (PRF1) in 20-50% of patients. In this patient, this mutation was responsible for a lack of protein expression using immunohistochemistry. If the pathologist thinks to look for it, this lack of expression can help clinicians make an early diagnosis of familial lymphohistiocytosis, even before molecular results.

In this patient, given the noisy clinical picture, the clinically suspected diagnosis was lymphoma. A medullary lymphocytic infiltrate in the context of MAS also raised the suspicion of T-cell lymphoma, especially as this diagnosis could not be formally ruled out on the molecular level due to a non-contributory clonality study. This presentation reminds pathologists to be particularly cautious before evoking the diagnosis of T-cell lymphoma in

the presence of a T lymphocytic infiltrate in the marrow, a fortiori in a young patient, and without any formal phenotypic or molecular argument.

EA4HP24-LYWS-295

Recurrent EBV+ diffuse large B-cell lymphoma in a patient with tubular aggregate myopathy muscular dystrophy and associated primary immunodeficiency disorder

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Case Description

The patient is a 69-year-old male with tubular aggregate myopathy muscular dystrophy, diagnosed approximately 30 years prior, also affecting his father and resulting in disability. He has associated primary immune deficiency with history of internal shingles, EBV+ diffuse large B-cell lymphoma and multiple basal and squamous cell carcinomas. At presentation, he was on therapy with pembrolizumab for invasive squamous cell carcinoma involving the ear. The EBV+ DLBCL was diagnosed 10 years prior, involving the right neck and in remission following chemotherapy (R-CHOP) and radiation. He now presents with a posterior scalp lesion of approximately 1 month with bleeding, occasional fever, night sweats and 60 lb weight loss while undergoing a procedure for the SCC complicated by pneumonia.

Biopsy Fixation Details

Formalin fixed, paraffin embedded

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections of skin show a focally ulcerated epidermis with an atypical lymphoid infiltrate extensively involving the superficial and deep dermis. The epidermis is otherwise spared. There are numerous large, atypical cells vesicular chromatin, prominent nucleoli and moderate eosinophilic cytoplasm. Mitotic figures are frequent. There are variably interspersed inflammatory elements.

Immunophenotype

The atypical lymphoid cells are positive for CD19, CD20 (variable), CD30 (80%), CD79a, PAX5, MUM1, c-Myc (>40%), EBV LMP1 and by CISH for EBER with kappa restriction by ultrasensitive CISH for kappa and lambda. Negative for CD10, CD43, CD56, CD138, Bcl2, Bcl6, EBNA2 and HHV8 LANA1.

Cytogenetics

FISH: Negative for *BCL2*, *BCL6* and *MYC* rearrangements

Molecular Studies

GenPath Onkosight NGS:

TET2 c.4913C>G and c.4165C>T VAFs: 33%, 35%

STAT3 c.1919A>T, VAF 33%

Muscular dystrophy panel consented

Proposed Diagnosis

EBV+ DLBCL, NOS (ICC)

EBV+ DLBCL, EBV+, inborn error of immunity (tubular aggregate myopathy) (WHO-HAEM5)

Interesting Feature(s)

The mechanism underlying his rare genetic disorder is interesting, resulting in both muscular dystrophy and primary immune deficiency. Tubular aggregate myopathy is caused by mutations in *ORAI1* or *STIM1* (usually autosomal dominant), resulting in tubular aggregates in skeletal muscle, likely related to altered Ca2+ signaling. This pathway is also key to lymphocyte activation. STIM1 regulates calcium influx by sensing ER Ca2+ levels and activating the Ca2+-release–activated Ca2+ channel, of which ORAI1 is a subunit. Autosomal recessive mutations in *ORAI1* cause hypotonia and severe combined immunodeficiency in mice (PMID 25227914). Patients have increased risk of infection with rare reports of EBV-associated lymphoproliferative disorders (PMID 20189884).

The question of whether altered Ca2+ signaling may affect risk of B-lymphomagenesis could also be considered given B-cell receptor activation, a key pathway and target in lymphoma, induces Ca2+ signaling. The connection to EBV is also intriguing: Ca2+ signaling regulates EBV lytic cycle activation (blocked by calcineurin inhibitors) and EBV latent proteins can modulate Ca2+ levels (PMID 34625709).

The mutational profile with *STAT3* and *TET2* mutations may raise the specter of a T or NK-cell lymphoma, which often present in the skin, but are reported in EBV+ DLBCL. *TET2* mutations clustered in the elderly (PMID: 36812290). *STAT3* mutations are frequent in HIV-associated large B-cell lymphomas (27%, Chapman et al. PMID 34272731), raising a question of potential association with the immune deficiency setting. DLBCL with *STAT3* mutations also appear to show increased CD30 (>20% of cells, Ohgami et al. PMID 24837465) as seen in this case.

EA4HP24-LYWS-299

EBV+ T-cell lymphoproliferative disorder in a paediatric patient with germline*TNFAIP3* mutation and Pompe disease.

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Case Description

Female, 9 years old, Libian patient presented with fever, uveitis, episodes of chorea, pericardic efflusion, oral ulcerative lesions, inguinal herpetic lesions, anemia, thrombocytopenia, increased ESR, CRP and ferritin. Autoimmunity screening was negative. She had splenomegaly, CNS white matter lesions suspicious for vasculitis and multiple lymphadenopathies. EBV tests were positive (antiVCA IgG+, IgM+; antiEBNA IgG+; antiEA IgG+; DNA of 10.773.000 copies/mL on blood). She was HLA-B51+. Germline exome sequencing revealed *GAA* mutation characteristic of Pompe disease and a *TNFAIP3* mutation (also known haploinsufficiency of A20). The clinical diagnosis was of a Bechet-like autoinflammatory disease. A lymph node biopsy was performed to exclude a lymphoproliferative disorder.

Biopsy Fixation Details

Formalin-fixed 10%, 24 hour.

Frozen Tissue Available

Not.

Details of Microscopic Findings

Lymph node showed partial architectural effacement. Cortical zone showed small B follicles, small and some atrophic GC, preserved mantle cells. Paracortical zone showed small to some medium size lymphocytes, some plasma cells and scattered eosinophils. The capsule was thickened, fibrotic and populated by small to medium size cells, without atypia, all around the lymph node, that also massively extended to the perinodal adipose tissue.

Immunophenotype

Capsular and perinodal cells were T-cells CD3+, CD4+, CD8-, CD2+, CD5+, CD7-, BCL2-, CD10-, BCL6-, PD1-, TIA1+/-, GranzimeB-, Perforin-, CD56-, CD30-, ALK1-, and they were EBV+ (EBER+, rare LMP1+, EBNA2-). Ki67 was 5-10%. Furthermore, there was a phenotypically normal nodal T cell population (CD3+, CD7+, partly CD4+ and CD8+, EBER-). Cortical B follicles showed normal immunophenotype.

Cytogenetics

Not done.

Molecular Studies

IgH and IgK: **Polyclonal**; TCRgamma: **Clonal** (courtesy of Dr. ESG D'Amore)

NGS (on lymph node): **STAT3** and **TET2** mutation (both probably pathogenic, low allelic frequency - VAF) (courtesy of Prof. Dr. L. Quintanilla-Fend)

Proposed Diagnosis

EBV+ T-cell lymphoproliferative disorder (CD4+), clonal, without atypia and with low Ki67. Important integration with clinical data to make the differential diagnosis between an EBV+ T LPD arised in a context of immunodeficit or immune system dysregulation and systemic chronic active EBV disease – CAEBV.

Interesting Feature(s)

The patient had a germline heterozygous mutation in ***TNFAIP3*** with maternal segregation (VUS 3). Mutation in *TNFAIP3* (also known haploinsufficiency of A20 - HA20) causes autoinflammation, autoimmune symptoms and Behcet´s disease-like symptoms. The same variant of our patient has been reported (PMID:31175876). It is not clear whether HA20 and CAEBV are related, and this case could represent this possibility. There are single reports of associations of HA20 and EBV persistent viremia (PMID: 30810840), but not with EBV+ T cells LPDs.

The significance of *STAT3* and *TET2* variants at low VAFs is not clear. In CAEBV are described mutations mainly in *DDX3X*, but also *TET2* mutations have been rarely reported (PMID: 30664667). *STAT3* mutations may play a role despite it has not been reported.

The patient has been treated with immunosuppressive therapy and anti-EBV lymphocytes until January 2024, but therapy didn't control the EBV DNA load and the symptoms. The patient also had worsening of peripheral neuropathy. Cerebrospinal fluid was positive for CD3+, CD4+, EBER+ T-cells.

The clinicians are evaluating the possibility of HSCT; the major limit is the heart impairment, and making an endomyocardial biopsy is under decision to clarify if the heart damage is due to the Pompe disease or to an EBV myocarditis.

EA4HP24-LYWS-305

An unusual tonsil lymphoproliferation

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Case Description

3 year-old female; Recurrent ENT infections (sinusitis, otitis). Adenoidectomy at 2 years. Growth curve break at 18 months.

Hypogammaglobulinemia with hyperIgM : (IgA, 0.06g/l (N 0.33); IgG : 0.07 g/l (N 4.82), IgM 3.6 g/l (N 1.43).
Ig Supplementation inducing a better growth curve.
No systemic infections
Bilateral tonsil enlargement
Tonsillectomy : Symetric enlargement of the left and right tonsil (2.5 cm in their larger axis)
One tonsil block.

Biopsy Fixation Details

Buffered Formalin fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Atypical follicular hyperplasia with disrupted germinal centers
Attenuated mantle zone
Polymorphic Expansion of the interfollicular area

Immunophenotype

Interfollicular polymorphic infiltrate of B and T cells with B immunoblasts and numerous Ki67 positive cells
Increase of intrafollicular and extrafolllicular CD4 +PD1+ and CXCL13 T cells
Increase of interfollicular IgM + B cells and decrease of Ig A and IgG plasma cells
No expansion of EBER positive cells

Cytogenetics

No

Molecular Studies

Absence of clonal rearrangement of IgH, Kapppa and TCR gamma genes in the tonsil . Immune deficiency linked to a Heterozygous dominant mutation of *PI3KR1* not present among the parents and siblings

Proposed Diagnosis

Tonsil lymphoproliferation due to an Activated PI3Kinase delta Syndrome (APDS) type 2 (mutation of PI3KR1)

Interesting Feature(s)

- rarity of these cases
- We reported a series of 36 patients with APDS2; (E Elkaim, B. Neven, J. Bruneau et al, JACI, 2016, 138, P210-8)
- Combination of histopathological elementary lesions in the follicular and interfollicular areas are suggestive of this entity.

such as : small B-cell follicles with atrophic mantle and expansion of IgM positive interfollicular cells; polymorphic B and T immunoblastic interfollicular expansion with numerous CD4+ PD1+ T cells with an "AITL like pattern¨.

EA4HP24-LYWS-329

EBV-positive Burkitt Lymphoma in the setting of CVID

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Case Description

A 49-year-old male patient presented with extended cervical and inguinal lymphadenopathy. In the CT scan, lymphadenopathy, retroperitoneal bulky disease and splenomegaly was detected, highly suspicious for lymphoma infiltration. CT-guided needle biopsy of the retroperitoneal disease and histological work-up was done. Clinical staging was completed (stage IVB).

The patient had a history of common variable immunedeficiency (CVID) which presented with leukopenia, thrombopenia and autoimmune hemolytic anemia and was treated with steroids and cyclosporin A.

Biopsy Fixation Details

FFPE material

Frozen Tissue Available

no

Details of Microscopic Findings

H&E staining of the core biopsy shows a diffuse infiltrate of monomorphic, medium-sized blastoid lymphoid cells with open chromatin, basophilic cytoplasm with inconspicuous nucleoli. Abundant mitoses and apoptosis can be appreciated. A starry sky pattern is not observed.

Immunophenotype

The tumor cells show strong positivity for CD20, CD10, BCL6 and MYC. MUM1 and BCL2 remain negative. EBV in situ hybridization is positive in nearly all tumor cells. LMP1 and EBNA2 are negative, consistent with EBV latency type I.

Cytogenetics

FISH analysis MYC BAP showed a break, BCL2 and BCL6 BAP probes wild type. 46, XY

Molecular Studies

Clonality demonstrated a clonal B-cell population in FR2 and FR3.

NGS mutational analysis revealed mutations (cDNA; VAF%) in *TP53* (c.524G>A; 19.5%), *MYC* (c.490C>G; 38.72%), *ID3* (c.241C>T; 15.46%), *TCF3* (c.1653T>A; 9.06%) and *GNA13* (c.977T>C; 72.94%).

Proposed Diagnosis

EBV+ Burkitt lymphoma in a patient with CVID

Interesting Feature(s)

This is a case of an EBV-associated Burkitt lymphoma (BL), occurring in the setting of immunodeficiency (CVID). According to the literature, the most frequent malignancies arising in patients with CVID are lymphomas and gastric adenocarcinomas. In several studies, the most frequent lymphomas are diffuse large B cell lymphoma, classic Hodgkin

lymphomas and marginal zone lymphomas (MALT-type). EBV positivity is described only in small subsets of cases, under 10% of the collected cases.
BL is subdivided into endemic, non-endemic/ sporadic and immunodeficiency-associated type. For the endemic type, EBV-positivity is the rule. Non-endemic type can be EBV positive in around 20% and immunodeficiency-associated BL can be positive in 30%. Interestingly, we found only one case report in the literature that describes a BL in the setting of CVID, which was EBV-negative.
More recently, it has been proposed to divide BL according to the association with EBV or not. Supportive for this is the fact, that differences in gene expression profile and mutational status have been described in recent years for EBV+ and EBV- cases, regardless of the setting (endemic/ non-endemic/ immunodeficiency-associated).
The encountered mutations in our case are characteristic of BL. According to the cohort investigated by Grande and colleagues, mutations in *MYC* are nearly equally distributed among EBV-positive and EBV-negative cases. However, the gene mutations identified in our case (*TP53*, *ID3/TCF3 and GNA13)* are significantly more frequent in EBV-negative cases. The mutations that are more frequently identified in EBV-positive cases are *ARID1A, DDX3X*, *ETS1* as well as genes involved in epigenetic regulation, that were not present in our case.
In summary this is a case of EBV+ BL in a patient with CVID that responded well to therapy and that is in complete remission 10 years after the initial diagnosis.

EA4HP24-LYWS-336

Atypical polymorphous lymphoproliferative disorder involving a spinal epidural mass in the setting of CTLA4 haploinsufficiency

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Case Description

A 22-year-old female with a complex medical history, including a presumptive diagnosis of CTLA4 haploinsufficiency (per prior history, confirmation in progress), presented with worsening numbness in her leg after lifting heavy objects. An MRI of the lumbar spine revealed a 4.7 x 1.4 x 0.9 cm posterior epidural mass, leading to a biopsy. Notably, she has a prolonged history of diffuse lymphadenopathy, splenomegaly, and evidence of autoimmune cytopenias, including immune thrombocytopenia (ITP) and autoimmune hemolytic anemia. Previous procedures include multiple bone marrow biopsies, as well as left cervical and right inguinal lymph node biopsies. The latter indicated follicular and interfollicular hyperplasia with increased sinus histiocytes. Past workup involved negative T and B cell clonality studies and an ALPS workup showing mildly elevated double-negative T-cells, negative apoptosis assay, and negative classic ALPS gene mutations. Quantitative

immunoglobulins in 2010 and 2013 revealed elevated IgG, but recent results show an elevated IgM level. Testing also indicated diminished class switch memory B-cells, increased CD4+ memory T-cells, and activated T-cells with HLA-DR expression.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

H&E-stained sections reveal multiple soft tissue fragments diffusely infiltrated by a mixed inflammatory cell population, comprising numerous plasma cells, histiocytes, mostly small lymphocytes, and scattered large immunoblastic cells. The background is characterized by hypervascularity and fibrosis. Focal clusters of histiocytes contain globular cytoplasmic material suggestive of immunoglobulin. While the infiltrate is extensive and dense, overt cytologic atypia is not apparent.

Immunophenotype

CD3 staining reveals numerous small T-cells, with CD4 highlighting the majority of T-cells and CD8 highlighting a minority (CD4>CD8, accompanied by a high number of PD1+ T-cells). CD20 highlights small B-cells (constituting about 20% of total cells) and scattered large immunoblastic cells. CD68 staining highlights numerous histiocytes. Ki-67 indicates a proliferation index of 30%. Scattered large immunoblastic cells are negative for ALK, CD10, CD30, and CD123. Plasma cells exhibit markedly skewed ratios in different sample foci, with extensive IgM staining and negative IgG staining. EBV (EBER-ISH) is negative.

Cytogenetics

N/A

Molecular Studies

Pending

Proposed Diagnosis

Atypical polymorphous (lymphoplasmacytic and histiocytic) proliferation, EBV-negative, reported history of primary immune deficiency.

Interesting Feature(s)

Cytotoxic T lymphocyte antigen 4 (CTLA4) plays a crucial role in immune homeostasis. Uniallelic germline mutations of CTLA4 leading to haploinsufficiency (CTLA4h) give rise to a phenotypically heterogeneous, immune-mediated disease characterized by neuroinflammation and the development of large, recurrent, multifocal, and inflammatory brain and spinal cord lesions, as recently described by Schindler et al., 2020. These lesions, characterized by an abundance of CD3+ T-cells, predominantly CD4+, variable B-cells, histiocytes/macrophages, and many plasma cells, also feature histiocytes with crystalline and globoid structures indicative of crystal-storing histiocytosis with higher IgM than IgG. The posterior epidural mass in this patient demonstrates nearly all the aforementioned histopathological features. Therefore, with a presumptive diagnosis of CTLA4 haploinsufficiency, her diagnosis aligns with a rare entity of CTLA4 haploinsufficiency neuroinflammatory disorder.

EA4HP24-LYWS-365

EBV-related proliferations (reactive hyperplasia and lymphoproliferative disorders) in a patient with common variable immuodeficiency (CVID)

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Case Description

This patient with no significant previous history presented at 12 y/o with neck lymphadenopathy. A LN biopsy led to a diagnosis of EBV+ CHL (images attached for retrospective review) followed by chemotherapy and radiation therapy leading to complete remission. At 14y/o, surveillance imaging studies found L axillary lymphadenopathy while she remained asymptomatic. An excisional biopsy (**workshop case**) showed reactive findings including follicular hyperplasia, paracortical hyperplasia, granulomatous inflammation and increased EBV+ cells. Surveillance imaging 1 year later showed R iliac lymphadenopathy; biopsy showed similar findings. EBV PCR showed 1789 copies/mcg. A workup for primary immunodeficiency was initiated and showed no/low non-protective IgG response toward Strep pneumoniae and Hib. She had low IgA, IgM and borderline low IgG. Lymphocyte transformation in response to mitogen stimulation was normal. A clinical diagnosis of CVID was made but sequencing of 207 genes related to primary immunodeficiency only found an *NOD2* variant that may increase risk of Crohn's disease and no other P/LP variants. She was started on IVIG. 11 years after the original lymphoma diagnosis, she developed R inguinal lymphadenopathy, an excisional biopsy showed findings consistent with EBV+ polymorphic B-cell LPD according to current criteria (images attached).

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Sections show a LN with largely intact nodal architecture. Follicular hyperplasia, paracortical hyperplasia and monocytoid lymphocyte hyperplasia are noted. There are increased epithelioid histiocytes forming non-caseating granulomas encroaching on germinal centers in areas.

Immunophenotype

CD20 and PAX5 highlight B cells within and outside the lymphoid follicles including scattered CD30-positive immunoblasts. The epithelioid histiocytes are positive for CD68, negative for CD1a and S-100. Kappa and lambda ISH highlight sparse plasma cells which

appear polytypic. EBER highlights many small and large positive cells. GMS and AFB stains are negative.

Cytogenetics

N/A

Molecular Studies

IGH/IGK gene rearrangement studies showed polyclonal gene rearrangements

Proposed Diagnosis

Lymph node with follicular hyperplasia, paracortical hyperplasia, granulomatous inflammation and increased numbers of EBV+ cells, in the setting of primary immunodeficiency

Interesting Feature(s)

Multiple biopsies from our patient show different morphologic findings that can be seen in lymphadenopathy of CVID patients. Reactive LNs of patients with CVID often show hyperplastic ill-defined germinal centers and granulomatous inflammation, which can be associated with EBV+ cells (our case) or other infections. Plasma cells can be found in the LNs though IgM-expressing cells tend to be the predominant isotype. The sometimes prominent granulomatous inflammation may be misdiagnosed as sarcoidosis. Besides reactive hyperplasia, EBV-related proliferations in CVID patients may be seen. Our patient developed an EBV-positive B-LPD 11 years after the initial diagnosis of CHL. Retrospective review of both specimens show similar morphologic features best classified as EBV+ polymorphic B-cell LPD with EBV positivity seen in a range of cell sizes. Definitive classification of EBV+ LPD in an immunodeficiency setting can be challenging due to overlapping morphologic features with EBV+ CHL and DLBCL in some cases. Our case highlights the importance of recognizing these unusual morphologic features; the findings in our patient's LN biopsies prompted the workup for primary immunodeficiency that established a diagnosis of CVID.

EA4HP24-LYWS-389

Peripheral T-cell lymphoma, not otherwise specified associated with *TET2* germline variant with mosaicism.

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Case Description

53-year-old male

Past medical history:

- Idiopathic thrombocytopenia 2005
- Common variable immunodeficiency 2009

- T-cell histiocyte rich large B-cell lymphoma 2010
- Waxing and waning lymphadenopathy (LAD) 2015-2022
- HPV positive cT3NxMx oropharynx squamous cell carcinoma 04/2022Current Presentation:
- Widespread LAD both above and below the diaphragm (Max SUV 11.6), splenomegaly and thrombocytopeniaHe underwent bone marrow (BM) biopsy (bx) (04/2022) and subsequent multiple lymph node (LN) biopsies (05/2022, 12/2022 and 09/2023).

Biopsy Fixation Details

The LN and BM core bx were fixed in 10% formalin, BM core was decalcified, and routinely processed.

Frozen Tissue Available

None

Details of Microscopic Findings

1) Paraaortic LN bx (12/2022):
Sections show diffuse lymphohistiocytic infiltrate composed of bland-appearing histiocytes, small and mature-appearing lymphocytes and rare intermediate sized lymphocytes with slightly irregular nuclear contours.
2) Retroperitoneal LN bx (09/2023):
Sections show diffuse infiltrate of intermediate to large atypical lymphoid cells with moderately abundant cytoplasm, irregular nuclei, vesicular chromatin, and variably distinct nucleoli.

Immunophenotype

1) Paraaortic LN bx (12/2022):
Immunohistochemistry: CD3+ T-cell predominant infiltrate with some scattered and loose clusters of CD20+ B-cells.
Flow cytometry: Atypical CD4/CD8 Double Negative T-cell population representing 7.0% of WBC with dim CD5 and TCRCbeta1 restriction (monotypic positive)
Normal: CD2, CD3, CD7, CD26, CD38, CD45
Negative: CD4, CD8, CD10, CD14, CD25, CD56, CD279 (PD1), TCR gamma/delta.

2) Retroperitoneal LN bx (09/2023):
Immunohistochemistry: The neoplastic cells
Express: CD3, CD2, TIA1, Granzyme B, GATA3 (weak, subset), p-STAT3
Do not express: CD20, CD4, CD5, CD7, CD8, CD10, CD30, CD56, T-Bet
Other: Ki67 proliferation index is 70-80% in the large atypical cells.
Flow cytometry: Abnormal T-cell population
Abnormal: CD3 (bright), CD5 (negative), CD7 (negative), CD38 (bright), CD45 (bright), TCRCB1 (restriction - monotypic positive), Forward Scatter (increased), Side Scatter (increased)
Normal: CD2, CD26
Negative: CD4, CD8, CD10, CD14, CD25, CD56, CD279 (PD1), TCR gamma/delta

Cytogenetics

NA

Molecular Studies
BM (04/2022) unmatched testing: *TET2* (E1433Gfs*45) VAF 51% suspicious for a germline alteration
Reference lab germline testing (07/2022): Negative
Nail as normal germline control for Matched IMPACT testing
(06/2023): *TET2* (E1433Gfs*45) VAF 26%
Retrospective reanalysis of germline testing from the fibroblast culture:
TET2 (E1433Gfs*45) ~3% of reads
These findings strongly suggested *TET2* (E1433Gfs*45) germline variant with mosaicism
Retroperitoneal LN (09/2023) matched testing: *DDX3X, ABL1, ARID4A, ETV5, RPS15*
Proposed Diagnosis
1) Paraaortic LN Bx (12/2022): Atypical lymphohistiocytic proliferation with Autoimmune Lymphoproliferative Syndrome (ALPS) like phenotype associated with *TET2* germline variant with mosaicism
2) Retroperitoneal LN Bx (09/2023): Peripheral T-cell lymphoma, not otherwise specified associated with *TET2* germline variant with mosaicism
Interesting Feature(s)
This case highlights the complexities and intricacies of germline testing and analysis.
Germline *TET2* mutations have been reported to be associated with ALPS-like proliferations.
This case shows the complete spectrum and evolution of the lymphoproliferative disorders associated with germline *TET2* mutations as additional somatic mutations are acquired triggering lymphomagenesis.
Diagnostic challenge: ALPS-like proliferation vs T-cell Lymphoma

EA4HP24-LYWS-413

Atypical B-cell proliferation in a patient with germline RAG2 variant

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Case Description
31-yo female presenting with cervical lymphadenopathy. Her past medical history is notable for primary immunodeficiency syndrome characterised
by hypogammaglobulinaemia, recurrent sinopulmonary infections, autoimmune sequelae (including refractory AIHA and vitiligo) and cholangitic liver disease. Genetic studies have identified heterozygous hypomorphic RAG2 mutations and likely represents a CVID. She had three biopsies of a cervical lymph node, intraparotid lymph node and most recently cervical lymph node excision. All samples showed atypical features but have been inconclusive for lymphoma. No plasma cells were demonstrated

morphologically or immunohistochemically and clonality testing on all three samples had failed. A cervical lymph node excision was performed:
A bone marrow biopsy (not included) performed showed maturing trilineage haematopoiesis with reactive features and CD8 positive T-cell lymphocytosis, with variable CD57 expression and oligoclonal T-cell rearrangements.The patient passed away from sepsis 6 month following the lymph node biopsy.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sections showed an enlarged lymph node with altered architecture and vague nodularity. The sinuses were obliterated. There were many irregularly shaped germinal centres which were composed of centrocytes, centroblasts, follicular dendritic cells and tingible body macrophages, and did not show obvious mantle layers, but instead were surrounded by a thick layer of monocytoid cells with irregular nuclei, condensed chromatin and moderate clear cytoplasm. Plasma cells were absent.

Immunophenotype

CD20, CD79a and CD19 highlight B-cells within serpiginous interconnecting follicles, which are additionally highlighted by underlying expanded follicular dendritic meshwork. CD3 highlights numerous interfollicular T-cells. CD5 and CD43 highlight a similar pattern to that of CD3. CD10 and BCL-6 highlight the germinal centre cells, although CD10 appears to be positive in only a subset of them. BCL-2 is negative in the germinal centres. IgD is negative. Ki-67 highlights a high proliferative index in the germinal centres and is 10% in the interfollicular area. Cyclin D1 and EBER were negative.

Cytogenetics

FISH analysis for BCL2, BCL6 and MALT1 revealed no split signal in >100 cells assessed.

Molecular Studies Clonality testing has been repeatedly attempted on this material as well as previous biopsies, but has been unsuccessful, which could be the result of a germline configuration of the immunoglobulin genes, a phenomenon that has been previously described in CVID.
NGS showed TP53 p.(Arg248Pro) NM_000546.6:c.743G>C Allele Burden: 18% Classification: pathogenic.

Proposed Diagnosis

Lymph node, cervical, excision:-Atypical lymphoid hyperplasia (See note)
Note: The overall findings are concerning due to the altered nodal architecture, including irregular follicles and increased marginal zones. While this could represent a marginal zone lymphoma, the possibility of B-cell hyperplasia (specifically marginal zone hyperplasia), cannot be excluded, especially in light of the underlying primary immunodeficiency. Clonality testing has been repeatedly attempted on this material as well as previous biopsies, but has been unsuccessful, which could be the result of a germline configuration of the immunoglobulin genes, a phenomenon that has been previously described in CVID. ifically marginal zone hyperplasia), cannot be excluded, especially in light of the underlying primary immunodeficiency.

Interesting Feature(s)
Lack of amplifiable gene rearrangements, unusual morphology

EA4HP24-LYWS-418

EBV-positive B cell lymphoproliferative disorder presenting with systemic and digestive disease in a patient with an Activated phosphoionositide-3 kinase delta syndrome (APDS)

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Case Description
A 30-year-old patient was followed, since the age of 4, for hypogammaglobulinemia. He was treated by immunoglobulin replacement since childhood. During childhood, he had disclosed several episodes of enlarged lymph nodes, without definitive diagnosis but with a spontaneous favorable outcome. Activated phosphoionositide-3 kinase delta syndrome (APDS type 1) due to *PIK3CD* heterozygous gain of function mutation (GLU1021LYS) was diagnosed when he was 28 years old. This mutation is responsible for a constitutive activation of the PIK3 pathway, including mTOR signaling.
In June 2023, he was admitted for cervical and inguinal lymphadenopathies, associated with hepatosplenomegaly, ileocaecal hypermetabolic mass (SUV of 19 on the PET-CT), weight loss, fatigue, sweat and diarrhea. Biological tests disclosed an inflammatory syndrome and the EBV load in total blood was 2.56 log UI/ml. A cervical lymph node was surgically removed and biopsies of the colonic lesion were performed.
Biopsy Fixation Details
Formalin
Frozen Tissue Available
None
Details of Microscopic Findings
The lymph node biopsy revealed hyperplastic follicles with large variably defined germinal centers with often attenuated follicular mantle zones. Other germinal centers were disrupted and partially effaced by small lymphocytes. The interfollicular zones were composed of small slightly irregular lymphoid cells admixed with scattered large cells, some with an irregular nucleus and a large nucleolus, resembling Hodgkin cells. There were areas of monocytoid B cells. Only few plasma cells were present, and eosinophils were absent.

On the colon biopsies, the mucosa was densely infiltrated by lymphoid cells, composed of small slightly irregular lymphocytes admixed with scattered large cells, Hodgkin or Reed-Sternberg-like cells and rare eosinophils.

Immunophenotype

In the lymph node, the follicles were CD20-positive with reactive germinal center (BCL2-, CD10+). The interfollicular small lymphocytes presented a T phenotype and were predominantly CD4 positive, less frequently CD8 positive. These T cells disrupted and partially destroyed some germinal centers. In the interfollicular zones, the large cells showed a B-cell phenotype (CD20+) and the Hodgkin-like cells were CD30+, CD15-, CD20+, PAX5+, OCT2+ and EBER positive. The HHV8 and CMV immunostainings were negative.

Cytogenetics

None

Molecular Studies

By PCR, no B-cell clone was identified and a T-cell clone of uncertain significance was found on lymph node biopsy.

Targeted NGS (lymphomas B & T) is ongoing.

Proposed Diagnosis

EBV-positive B cell lymphoproliferative disorder presenting with systemic and digestive disease in a patient with an Activated phosphoionositide-3 kinase delta syndrome (APDS).

Interesting Feature(s)

We describe a case of a EBV positive B cell lymphoproliferative disorder in the lymph node and digestive tract of a patient with a PI3K delta syndrome (PIK3CD mutation) (APDS). This immunodeficiency is very rare and is known to predispose to EBV driven aggressive lymphomas and EBV+ positive lymphoproliferation but only few cases with histopathological data are reported in the literature. Presence of EBV-positive “Hodgkin-like” cells in this context even with a systemic presentation with an intestinal mass should not be misdiagnosed as a Hodgkin lymphoma.

The patient was given Leniolisib, a PIK3CD inhibitor, and he turned asymptomatic, 3 weeks after onset of treatment.

EA4HP24-LYWS-425

Bone marrow findings of autoimmune lymphoproliferative syndrome

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Case Description

A 44-year-old-man came to our hospital due to gingival bleeding and blood tests revealed thrombopenia (9 x $10^{3/}$ µl), initially considered as autoimmune trhombocytopenic purpura. Patient did not present lymphocytosis at peripheral blood. CT scan detected numerous slightly enlarged lymph nodes, not suggestive of lymphoma. Determinations for CMV and EBER were negative.

Corticosteroids therapy was initially ineffective and subsequent bone marrow biopsy was performed.

Biopsy Fixation Details

Paraffin embeded tissue. Formol 10%

Frozen Tissue Available

Peripheral blood available at hematology department

Details of Microscopic Findings

Bone marrow smears showed hematopoietic cellularity of three series with preserved morphology and lymphocytosis of mature appearance.

Bone marrow biopsy was normocelular and showed preserved hematopoietic cellularity and increased medium-sized T-cell lymphocytes with clear cytoplasm within an interstitial and paratrabecular pattern.

Immunophenotype

By flow, 49,80% of the cells of bone marrow corresponded to mature-T- lymphocytes with CD45++/CD3++/CD5++/ TCR$\alpha\beta$+/CD56-, 35% of which were CD4-/CD8-, not suggested of lymphoproliferative disease. Hematopoietic cells did not show either aberrant profile of antigenic differentiation and CD34+ myeloid blasts were <1% of total cells.

By immunohistochemistry lymphocytes were CD3+/CD57+/TCRBETA+/PD1+ and negative for CD4, CD8, TDT, Granzyme, TIA1, TCRGAMMA, PSTAT3, PSTAT5, P53 and EBER.

Cytogenetics

Deletion of 5q and 7q were not detected by FISH studies (Metasystem).

Molecular Studies

Initial molecular studies performed in peripheral blood detected oligoclonal rearragangement of TCRGAMMA (PCR).

Next-generation sequencing (NGS) study with a customized panel for T-cell lymphomas (Sure Select XT HS, Agilent Techonologies) was perfomed on bone marrow tissue and detected a mutation of uncertain significance (VUS) at *JAK1* gene (c.1819G>T; p.Asp607Tyr; VAF 47%).
After case discussion (see section below) NGS study on peripheral blood cells was performed using a panel of 434 genes related to primary immunodeficiencies (MiSeq, Illumina), and c.905_924dupAAAATTCAAACTTCAGAAAT/p.Glu309Lysfs*38 heterozygous variant of *FAS* gene was detected (VAF: 53.1%)., confirming autoimmune lymphoproliferative syndrome (ALPS) diagnosis

Proposed Diagnosis

Based on previously described findings, a diagnosis of T-large granular lymphocytic leukemia (T-LGLL) was initially considered. T-LGLL consists on CD8+/ TCR$\alpha\beta$+, CD4+/ TCR$\alpha\beta$+ or rarely CD4-/CD8-/TCR$\gamma\delta$+ lymphocytes. Furthermore, at bone marrow histology T-LGLL usually shows interstitial CD4+ lymphoid aggregates within CD8+ intrasinusoidal lymphocytes.Regarding our case, clinical presentation, double negative immunophenotype of T-cell lymphocytes and lack of clonality of TCR prompted us to reconsider this diagnosis, suggesting ALPS syndrome and NGS study for primary immunodeficiencies was required

Interesting Feature(s)

ALPS syndrome is a rare disorder of immune dysregulation characterized by heterozygous mutations within *FAS* signanling pathway, with unknown incidence. Nearly 500 patients from 300 families have been reported to date.
Our case presented typical clinical findings with non-malignant lymphadenopathy, splenomegaly and immune-mediated cytopenias affecting any lineage.
Our case also highlights typical histopathological findings on bone marrow biopsy with increased number of double negative T-cells of paratrabecular location. In this context, immunophenotype and pattern of infiltration may be of help to distinguish ALPS from T-LGLL. Subsequent molecular studies are decisive to render a definitive diagnosis.

EA4HP24-LYWS-438

Bilateral conjunctival marginal zone lymphoma in a prepubescent child with constitutional CTLA4-mutation

Dr. Jens Enoksson[1], PhD/MD Mats Ehinger[2]

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Case Description

·6-year-old boy presenting in spring 2023 with bilateral gelatinous conjunctival masses, pinkish-pale in color, varying in volume over time. The lesions had been present approximately 1 year with preserved visual acuity.

•A differential count of the peripheral blood revealed no aberrations
•No bone marrow smear was performed
•No bone marrow biopsy was performed
•Diagnostic biopsies from bilateral tumors of the conjunctivae was performed

Biopsy Fixation Details

Formalin-fixed (10%), paraffin embedded biopsy

Frozen Tissue Available

No

Details of Microscopic Findings

Conjunctival tissue with overlying epithelium, and in the stromal tissue expanded lymphoid areas with expanded follicles/germinal centers without clear mantle zones but with small surrounding cells with somewhat clear cytoplasm.

Immunophenotype

CD20+/CD10-/CD5-/ BCL-6

Cytogenetics

N/A

Molecular Studies

Multiplex PCR showed monoclonal rearrangemants of the IgH- and IgK-genes.
Whole genome sequencing of peripheral blood: Heterozygous missense variant in CTLA4-gene: Chr2(GRCh38):g.203870685G>A;NM_005214.5(CTLA4):c.209G>A;p.(Arg70Gln). HGVS: c.[209G>A];[=].

Proposed Diagnosis

Constitutional missense variant of the CTLA4-gene with subsequent development of small B-cell lymphoma of the conjunctivae, most likely marginal zone lymphoma.

Interesting Feature(s)

To the best of our knowledge this is the first description of a missense variant in the CTLA-4-gene that is likely to be involved in the pathogenesis of this rare lymphoma of the conjunctiva in a child. The case highlights the central role of the immunomodulator CTLA-4 not only to prevent autoimmunity and hyperactivity of the immune system, but also in the immunosurveillance to prevent cancer development.

EA4HP24-LYWS-450

Necrotizing Lymphadenitis in the setting of Atypical Germline GATA2 Mutation

Dr. Bhaumik Shah, Dr. Peter Abdelmessieh, Dr. Yavuz Sahin, Dr. Nicholas Mackrides, Dr. Yue Lynn Wang, Dr. Reza Nezati, Dr. Mariusz Wasik

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Case Description

40 year old male presented to our institute in April 2022 for the evaluation of recurrent cyclic fevers and night sweats started after bone marrow biopsy performed for the new diagnosis (Feb 2022) of chronic myeloid leukemia (CML). He also developed cough with non-productive sputum. Chest CT scan showed interlobular septal thickening with centrilobular ground glass opacites in the left lung, multistation mediastinal and hilar lymphadenopathy and left para-aortic nodal mass (4cm). Excised paraaortic lymph node showed extensive necrotizing lymphadenitis. Molecular studies on para aortic lymph node, peripheral blood and bone marrow identified germline GATA2 mutation. Infectious and autoimmune work up was negative except mycobacteriaum avium intracellulare (MAI) grown on the culture from bronchoalveolar lavage. Patient required multiple hospitalizations with pulmonary alveolar proteinosis and unexplained recurrent fevers without unifying diagnosis. Currently, the patient is awaiting stem cell transplant.

Biopsy Fixation Details

Formalin Fixed Paraffin Embedded

Frozen Tissue Available

No

Details of Microscopic Findings

Excised paraaortic lymph node showed an extensive necrosis containing predominantly neutrophils and numerous histiocytes with abundant intracytoplasmic cellular debris and intact granulocytes.

Immunophenotype

S-100,CD68,CD163, BCL1 highlight numerous histiocytes with abundant intracytoplasmic neutrophilic debris and intact granulocytes.

Cytogenetics

Karyotype (blood): t(9;22)

Molecular Studies

NGS (275 gene panel): Paraaortic lymph node.
GATA2 p.Pro444Leu VAF - 46.5%
KMT2B p.Glu373del VAF-34.5%
MITF p.Arg255Gln VAF-47.4%
NFKBIA p.Ala190Val VAF-49.05.
Identical GATA2, MITF and NFKBIA variants are also present in peripheral blood and bone marrow.

Proposed Diagnosis

Necrotizing lymphadenitis in the setting of atypical germline GATA-2 mutation

Interesting Feature(s)

In our case, necrotic areas show marked neutrophilic infiltrate featuring karyolysis, pyknosis and abundant karyorrhectic debris admixed with numerous necrotic macrophages with intracytoplasmic nuclear debris. Adjacent areas show aggregates of macrophages with intracytoplasmic nuclear debris with many intact neutrophils and few lymphocytes mimicking emperipolesis. Atypical mycobacterial lymphadenitis typically show sheets of macrophages with abundant AFB+ bacilli, but no necrosis, granuloma, calcification or fibrosis seen with mycobacterium tuberculosis lymphadenitis. Kikuchi disease show crescent shaped histiocytes but no neutrophils. Rosai-dorfman disease can have increased IgG4+ plasma cells but not extensive necrosis with lysis of neutrophils within histiocytes. Although our patient had elevated sIL2R and ferritin suggesting macrophage activation, but no erythrophagocytosis. Absence of tender plaques and nodules exclude sweet syndrome. Dasatinib can cause significant adenopathy but not usually with necrosis or in setting of diffuse fevers. Immunodeficiency with marked susceptibility to infections including nontuberculous mycobacteria, predisposition to MDS/AML and pulmonary alveolar proteinosis are hallmarks of GATA2 deficiency (Spinner et al). Missense mutation in GATA variant of our case does not affect the charge of the amino-acid residue and its location on the C-terminal precludes effect on two zinc finger functional domains or the nuclear localization signal. Despite indications of benign GATA2 variant, the constellation of findings in our patient i.e. recurrent febrile neutropenia, pulmonary alveolar proteinosis, deep vein thrombosis, MAI of lung, CML, necrotizing lymphadenitis are compatible with phenotype of GATA deficiency.

Panel Diagnosis Session II

Panel Diagnosis: Syndrome with autoimmunity

Case	Panel diagnosis - underlying genetic defect	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-42	ALPS - *FAS*	Reactive	Typical case of ALPS
EA4HP24-LYWS-49	ALPS - *FAS*	NLPHL	CD4-CD8- T-cell of ALPS and CD4+CD8+ T-cells of NLPHL, emperipolesis
EA4HP24-LYWS-252	ALPS - *FAS*	Reactive	Initial diagnosis of TFH lymphoma
EA4HP24-LYWS-425	ALPS – *FAS*	Reactive	Bone marrow, initial diagnosis of T-LGL
EA4HP24-LYWS-66	Probable ALPS	SHML/ RDD	Associated with SHML/ RDD

Panel Diagnosis: Immune dysregulation

Case	Panel diagnosis - underlying genetic defect	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-162	*CVID*	1. Reactive; 2 and 3. NMZL	Progression of disease, sufficient for lymphoma
EA4HP24-LYWS-329	*CVID*	Burkitt lymphoma, EBV+	Burkitt only very rarely reported in CVID
EA4HP24-LYWS-365	*CVID*	Polymorphic LPD, EBV+	Earlier diagnosis of cHL
EA4HP24-LYWS-29	*CVID (TNFRSF13B)*	Reactive LPD	Difficult differential with lymphoma

EA4HP24-LYWS-180	*APDS1*	Reactive vs. EMZL	Multiple lesions
EA4HP24-LYWS-356	*APDS1*	Reactive	Cecal mass
EA4HP24-LYWS-418	*APDS1*	Reactive	Both lymph node and GI lesion
EA4HP24-LYWS-222	*APDS2*	B-cell lymphoma, NOS	Shows progression of disease, late diagnosis
EA4HP24-LYWS-231	*APDS2*	Reactive	Multiple reactive lesions, proliferation of PD1+ T-cells
EA4HP24-LYWS-305	*APDS2*	Reactive	Prominent proliferation of PD1+ T-cells intra- and extrafollicular
EA4HP24-LYWS-438	*CTLA4* haploinsuff.	MZL vs. reactive LPD	Bilateral conjunctival lesion

Panel Diagnosis: EBV susceptibility

Case	**Panel diagnosis - underlying genetic defect**	**Panel Diagnosis**	**Unusual Features**
EA4HP24-LYWS-12	*SH2D1A* (XLP1)	Fulminant EBV+ LPD	Rapid diagnosis with SAP flow cytometry
EA4HP24-LYWS-284	*SH2D1A* (XLP1)	HGBCL/LBCL-11q	Mutation found coincidentally
EA4HP24-LYWS-436	*SH2D1A* (XLP1)	DLBCL, EBV+	Multiple samples → progression of disease
EA4HP24-LYWS-119	*MAGT1* (XMEN)	EBV+ B-cell lymphoma with plasmacytic differentiation	Typical presentation with multiple infections
EA4HP24-LYWS-200	*MAGT1* (XMEN)	1. cHL, EBV- 2. Polymorphic LPD, EBV+	Diagnosis made after relapse

EA4HP24-LYWS-177	*ITK*	cHL, EBV+	Infectious complications of therapy
EA4HP24-LYWS-184	*RAB27A* (Griscelli syndrome)	HLH	Presentation at older age
EA4HP24-LYWS-288	*PRF1*	HLH	Lack of perforin staining
EA4HP24-LYWS-299	*TNFAIP3* (A20)	CAEBV	Uncertain relationship between TNFAIP3 mutation and CAEBV
EA4HP24-LYWS-389	*TET2* (mosaic)	1. Reactive, ALPS-like; 2. PTCL, NOS	EBV negative
EA4HP24-LYWS-293	*RIPK1*	Indolent ENKTL	Relevance of RIPK1 mutation uncertain

Panel Diagnosis: DNA repair

Case	**Panel diagnosis - underlying genetic defect**	**Panel Diagnosis**	**Unusual Features**
EA4HP24-LYWS-108	*ATM*	T-LBL, DLBCL	Multiple lymphomas
EA4HP24-LYWS-331	*ATM*	Lymphoplasmacytic proliferation, EBV-	Patient later developed DLBCL (not clonally related)
EA4HP24-LYWS-285	*ATM*	DLBCL, EBV+	Development of chronic EBV after treatment
EA4HP24-LYWS-336	*ATM*	Polymorphic LPD, EBV-	Presentation with epidural mass
EA4HP24-LYWS-37	*ATM* carrier	Reactive lymphoproliferation	Thyroid follicular hyperplasia
EA4HP24-LYWS-5	*NBS*	Near-ETP ALL	Earlier diagnoses of T-cell lymphoma and T-LBL
EA4HP24-LYWS-413	*RAG2*	Atypical lymphoid hyperplasia	Reactive vs. MZL

Panel Diagnosis: Combined immune deficiency with syndromic features

Case	Panel diagnosis - underlying genetic defect	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-207	*KMT2D* (Kabuki syndrome)	Reactive LPD	Initial diagnosis of CHARGE syndrome
EA4HP24-LYWS-295	*ORAI1/ STIM1* (Tubular aggregate myopathy)	DLBCL, EBV+	10 years prior also DLBCL, EBV+

Panel Diagnosis: Immunoactinopathies

Case	Panel diagnosis - underlying genetic defect	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-166	*WAS*	Reactive LPD, EBV-	Differential diagnosis with B-cell lymphoma
EA4HP24-LYWS-43	*ARPC1B*	EBV+ LPD	Initially considered to be WAS
EA4HP24-LYWS-178	*ACTB (NKD)*	EBV+ LPD, Hodgkin-like	NK-cell deficiency, presentation at older age

Panel Diagnosis: DNA repair

Case	Panel diagnosis - underlying genetic defect	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-189	*TET2*	Multiple lymphomas	Multiple lymphomas
EA4HP24-LYWS-7	*DDX41*	LPL	Patient also developed MDS
EA4HP24-LYWS-280	*PTPN13*	DLBCL, EBV-	Uncertain association between PTPN13 mutation and lymphoma
EA4HP24-LYWS-321	*PTEN*	T-cell LPD	T-LPD most likely due to

			sirolimus treatment
EA4HP24-LYWS-409	*SMARCA4*	T-LBL	Uncertain association between SMARCA4 mutation and lymphoma
EA4HP24-LYWS-450	*GATA2*	Necrotising lymphadenitis	Also CML with dasatinib treatment
EA4HP24-LYWS-130	*BRCA1*	B-LBL	Incidental finding, BCL2 rearrangement

Panel Diagnosis: No germline genetic defect

Case	**Panel diagnosis - underlying genetic defect**	**Panel Diagnosis**	**Unusual Features**
EA4HP24-LYWS-75	*GATA2* (somatic)	T-LGL	Turner syndrome
EA4HP24-LYWS-214	None	Marginal zone hyperplasia	Differential diagnosis of APDS, but mutation absent

LYMPHOMA SESSION III: Atypical lymphoproliferations associated with therapeutic intervention

Oral Presentations

EA4HP24-LYWS-379	Classical Hodgkin Lymphoma, EBV+ following immunomodulator (IL-23 inhibitor) therapy.
EA4HP24-LYWS-193	Atypical lymphoproliferation of non-canonical T follicular helper (Tfh) cells associated with etanercept and probably also with methotrexate therapy
EA4HP24-LYWS-208	HHV-6 Lymphadenitis with DRESS Syndrome – Another Lymphoma Mimic
EA4HP24-LYWS-172	EBV+ large T cell lymphoproliferative disorder following CART therapy for EBV+ diffuse large B cell lymphoma
EA4HP24-LYWS-262	Post-CD19-CAR-T therapy trans-differentiation of a transformed follicular lymphoma in to an undifferentiated malignant neoplasm of uncertain lineage.
EA4HP24-LYWS-26	Chronic lymphocytic leukemia with pseudo-Richter transformation consistent with recent interruption of ibrutinib
EA4HP24-LYWS-226	Dasatinib-associated lymphadenopathy

EA4HP24-LYWS-379

Classical Hodgkin Lymphoma, EBV+ following immunomodulator (IL-23 inhibitor) therapy.

Dr. Bhaumik Shah, Dr. Marcus Messmer, Dr. Nicholas Mackrides, Prof. Mariusz Wasik, PhD/MD Yibin Yang, Prof. Reza Nejati

Temple Health System, Fox Chase Cancer Center, Philadelphia, USA

Case Description

40 year-old obese male with a history of smoking, hypertension, chronic plaque psoriasis for 10 years and on Guselkumab (IL-23 inhibitor) for psoriatic arthritis since Dec 2022, presented to our institution in Aug 2023 for the second opinion for his outside diagnosis of atypical EBV-lymphoproliferative disorder based on core biopsy of right bulky cervical lymphadenopathy. PET-CT scan at our institution showed large hypermetabolic lymph node conglomerate (Level I-V; 8.2 x 4.3 x 8.8 cm) with SUV of 18.8. Excised level III lymph nodes at our institution showed Classical Hodgkin Lymphoma, Epstein Barr Virus (EBV)+, Iatrogenic/Therapy related. Patient completed 2 cycles of ABVD chemotherapy in Dec 2023. Post-treatment FDG-PET-CT showed deauville 2 complete response, and then received 20 Gy IMRT.

Biopsy Fixation Details

Formalin Fixed Paraffin Embedded

Frozen Tissue Available

No

Details of Microscopic Findings

Excised right cervical level III lymph nodes showed partial effacement of the nodal architecture by scattered and focally clustered, mononuclear to bilobed/multilobated large atypical cells (H+RS cells) with vesicular chromatin and large eosinophilic nucleoli, **predominantly in an interfollicular area** a in a background of variable mixture of small lymphocytes, histiocytes with scattered eosinophils and neutrophils.

Immunophenotype

The large atypical cells are p**ositive for PAX5 (weak), CD15 (subset), CD30, CD200, MUM1**, **PD-L1, EBER-ISH, CD79 (weak; subset) and n**egative for CD45, CD20, CD3, CD10, BCL6, BCL2, OCT2, BOB-1. CD79 is negative to stains weakly subset of RS+H cells. No clonal B-cells or aberrant T-cells by flow cytometry.

Cytogenetics

Cytogenomic microarray is negative for genomic imbalances.

Molecular Studies

NGS (275 gene panel) detected Tier 2 mutations: ATR splice site c.3819+1G>T (VAF - 57.1%) & POLE c.6730C>T (VAF - 47%).

Proposed Diagnosis

Classical Hodgkin Lymphoma, EBV+, Iatrogenic/Therapy-related.

Interesting Feature(s)

Biologic agents, IL-23 and IL-17 inhibitors are associated with a diminished risk of several malignancies, including non-hodgkin lymphoma. Literature is limited to one case of Hodgkin Lymphoma reported in a patient receiving Ustekinumab (IL(s)-23 and 12 ihibitor) for 2 months. Although, psoriasis is an independent risk factor for the development of malignancy, there is an absolute low-risk of developing lymphoma except Hodgkin Lymphoma. Extensive research data showed a dichotomous cellular and cytokine immune milieu in EBV+ versus EBV- Classical Hodgkin Lymphoma, with EBV positive Classical Hodgkin Lymphoma displayed Th1 immune microenvironment profile, while EBV negative classical Hodgkin Lymphoma manifested Th17 profile. Constitutive activation of NF-kB pathway is the central molecular step in Hodgkin Lymphoma pathogenesis. Our patient had symptoms of plaque psoriasis for nearly 10 years but he did not develop lymphadenopathy until after the initiation of immunomodular therapy. Few months after the Guselkumab therapy, patient started developing progressive lymphadenopathy, evident by syncope/fainting episodes due to the mass effect on carotid sinus. We attribute the role of IL-23 inhibitor towards development of the bulky lymphadenopathy. We hypothesize that immune dysregulation stemming from IL-23/IL-17 axis blockadge might have led to functional divergence to Th1 effector response due to plasticity of Th17 cells, creating favorable inflammatory microenvironment for EBV and constitutive activation of NK-fB pathway, leading to development of Hodgkin Lymphoma. If succeeded, the additional data from the work up of tumor microenvironment will be provided prior to the meeting.

EA4HP24-LYWS-193

Atypical lymphoproliferation of non-canonical T follicular helper (Tfh) cells associated with etanercept and probably also with methotrexate therapy

Dr. Jagmohan Sidhu

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Case Description

A 63-year-old female with a history of rheumatoid arthritis (RA), diabetes mellitus, CHF, COPD, coronary artery disease, dyslipidemia, and 50-pack-year smoking history was admitted with severe shortness of breath for 2 days. She was switched from methotrexate to etanercept and prednisone for RA about 2 months before admission. CT scans showed bilateral pulmonary emphysema, pleural effusions, probable right lower lobe pneumonia, extensive cervical, bilateral axillary & mediastinal lymphadenopathy. Bronchial culture detected influenza A. Pancytopenia appeared and persisted despite discontinuing etanercept. Left axillary lymph node (LN) was excised and sent fresh to pathology

department. LN measured 1.8 cm x 1.4 cm x1.0 cm. A piece submitted for flow cytometry & the rest was put in 10% neutral buffered formalin. Two days after the biopsy, she developed multisystem organ failure, and died.

Biopsy Fixation Details

10% Neutral Buffered Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

LN architecture is almost completely effaced by a diffuse infiltrate of monomorphic small lymphocyte & small blood vessel proliferation with hyaline fibrosis of capsule & parenchyma & patent subcapsular sinuses. There are no germinal centers, large cells, mitotic figures, hemorrhage or necrosis

Immunophenotype

Flow cytometric analysis: Cell viability is 85% & lymphocyte gate has 69% of total events. Most of the lymphocytes are CD4+/CD57+/CD200+ T cells.

Immunohistochemistry: Most of the lymphocytes are positive for CD2, CD3, CD5, CD7, GATA3, CD57, CD200, & Perforin, & are negative for CD10, BCL6, CXCL13, ICOS1, Granzyme, TIA-1, T-bet, CD56, & CD30. About 1-2% cells are CD138-positive plasma cells & background histiocytes are CD68-positive.

Cytogenetics

Not performed

Molecular Studies

In Situ Hybridization: Admixture of kappa & lambda mRNA+ve cells; Negative for EBER.

TCR Gene Rearrangement Studies: Negative

Proposed Diagnosis

Atypical lymphoproliferation of non-canonical T follicular helper (Tfh) cells associated with etanercept and probably also with methotrexate therapy

Interesting Feature(s)

1. Proliferation of CD4+/CD57+/CD200+/PD1+/GATA3+/CXCL13-/CD10-/ BCL6-/ICOS1- Tfh cells & proliferation of small blood vessels raising a concern for Tfh-cell lymphoma
2. Absence of immunoblasts, CD21+ve expanded follicular dendritic cell networks, EBV, & TCR gene rearrangement & 1-2% Ki67 labeling index rule out Tfh-cell lymphoma. Angioimmunoblastic T-cell lymphoma (AITL) & benign T-cell proliferation mimicking peripheral T-cell lymphoma have been reported in association with etanercept & methotrexate (*BMJ Case Rep. 2011;2011; doi:10.1136/bcr.05.2011.4245; Mod Rheumatol. 2013;23:817-822; Diagn Pathol 2008;3:13 doi:10.1186/1746-1596-3-13 ; Pathol Res Pract. 2010;206:9-13 doi:10.1016/j.prp.2009.03.005).*
3. GATA3 +ve/BCL6 -ve immunophenotype of Tfh cells is not like that of canonical-TFH cells, but is like “Th2-like Tfh-cell” subset (*Group 2 Tfh Cells* classified by Eisenbarth et al). (*Trends Immunol. 2021; 42:658–669. doi:10.1016/j.it.2021.06.003; J Immunol. 2004;173:68-78).*
4. Influenza A was detected by bronchial culture, but it cannot be the cause of lymphoproliferation because influenza A virus induces Th1 cell (GATA3-ve/Tbet+ve) proliferation *(Immunity. 2021;54:687-701.e4).*

5. Marked decrease in B cells because both etanercept & methotrexate suppress B cells (*Mod Pathol. 2009;22:15321540; Arthritis Rheumatol.2014;66:2590-2600; Biomed Pharmacother. 2003;57:278-281*).

EA4HP24-LYWS-208

HHV-6 Lymphadenitis with DRESS Syndrome – Another Lymphoma Mimic

Dr. Abdallah Flaifel[1], Dr. Joao V. Alves De Castro[1], Dr. Joseph Rocco[2], Dr. Elaine S. Jaffe[1]

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Case Description

A 20-year-old man on minocycline for acne, presented with 3 weeks of progressive fevers, neck swelling, and a diffuse, maculopapular rash on the trunk and extremities. Laboratory data showed elevated transaminases, lactate dehydrogenase, and leukocytosis of 34.3 cells/μL with marked eosinophilia of 28.8%. A CT scan revealed diffuse lymphadenopathy and hepatosplenomegaly.

The patient's constellation of symptoms including skin eruption, fever, hematologic abnormalities, and signs of liver dysfunction, were consistent with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, and suggesed widespread immune response.

Biopsy Fixation Details

Formalin fixed Paraffin Embedded tissue.

Frozen Tissue Available

Not available

Details of Microscopic Findings

Microscopic examination revealed disrupted lymph node architecture with marked paracortical expansion that contained numerous large mononuclear cells showing nuclear and cytoplasmic inclusions. The background included small lymphocytes, eosinophils, and histiocytes. Residual follicles were observed in the far cortex.

Immunophenotype

Immunohistochemical stains included CD3, CD20, CD5, CD7, CD4, CD8, CD19, CD79a, CD30, CD15, PAX-5, MUM-1, ALK, BoB-1, Oct2, ICOS, PD1, S100, and EMA. The large, atypical cells displayed positive immunostaining for HHV6 (Human Herpesvirus 6) in the cytoplasmic, but not nuclear inclusions. The lesional cells were CD3+ and co-expressed CD5 and CD7. CD4 was positive with a distribution suggesting positivity in the virally infected cells, but admixed CD8-positive cells were present. ICOS was positive in most lymphoid cells, while PD1 was negative.

CD20+ B cells were present in residual follicles, primarily localized to the far cortex.

Scattered CD30+ immunoblasts were present in relatively low numbers. Histiocytes and granulocytes demonstrated positivity for CD15. S100 highlighted expansion of dendritic cells in the paracortical reaction.

Cytogenetics

Not performed

Molecular Studies

PCR studies showed a polyclonal T-cell receptor gamma-gene rearrangement.

Proposed Diagnosis

HHV-6 Lymphadenitis with DRESS Syndrome

Interesting Feature(s)

While the exact mechanisms underlying DRESS syndrome remain elusive, there is evidence linking it with HHV6 lymphadenitis in some cases. Drug hypersensitivity reaction is a clinical trigger.

An association between HHV6 and Hemophagocytic Lymphohistiocytosis (HLH) has been noted. The involvement of HHV6 in CD4+ T-cells suggests a role in initiating or exacerbating HLH, especially in the setting of DRESS syndrome.

In this case lymphoma was initially suspected, prior to the recognition of the characteristic viral inclusions. High-dose prednisone was administered, resulting in a gradual symptom resolution over one month. To reduce steroid dependence and prevent relapse, corticosteroids were subsequently replaced with cyclosporine, offering a prolonged immunosuppressive treatment approach.

References:

1- Balakrishna JP, Bhavsar T, Nicolae A, Raffeld M, Jaffe ES, Pittaluga S. Human Herpes Virus 6 (HHV-6)-associated Lymphadenitis: Pitfalls in Diagnosis in Benign and Malignant Settings. American Journal of Surgical Pathology. 2018 Oct;42(10):1402-1408.

2- Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, Belaich S, Crickx B. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Archives of Dermatology. 2001 Mar;137(3):301-4.

EA4HP24-LYWS-172

EBV+ large T cell lymphoproliferative disorder following CART therapy for EBV+ diffuse large B cell lymphoma

Dr. Philip Bulterys[1], Dr. Timothy Miller[1], Dr. Mark Hamilton[2], Dr. Takeshi Sugio[2], Dr. Troy Noordebos[2], Shriya Syal[2], Dr. Zinaida Good[2], Sunita Patil[2], Adam Kuo[2], Moksha Desai[2], Shuyu Shi[2], Prof. Crystall Mackall[2], Prof. Maximilian Diehn[2], Prof. Ash Alizadeh[2], Dr. David Miklos[2], **Prof. Dita Gratzinger**[1]

[1] Stanford University School of Medicine, Pathology, Stanford, USA; [2] Stanford University School of Medicine, Hematology and Oncology, Stanford, USA

Case Description

The patient is a 59-year old woman with a history of EBV positive diffuse large B-cell lymphoma status post CAR-T therapy (Yescarta), presenting with ongoing pancytopenia, increasing EBV titer, and clinical findings consistent with hemophagocytic lymphohistiocytosis. A bone marrow biopsy is performed.

Biopsy Fixation Details

The bone marrow biopsy was fixed and decalcified in Bouin's solution (>2 hours) followed by Immunocal solution (3 hours), processed routinely, and embedded in paraffin.

Frozen Tissue Available

No

Details of Microscopic Findings

The peripheral blood showed pancytopenia. The aspirate smears showed scattered large atypical cells with blue cytoplasm and slightly irregular nuclear contours and scattered hemophagocytic histiocytes. Sections of the core biopsy showed sheets and nodules of large cells with variably abundant cytoplasm and irregular nuclear contours.

Immunophenotype

Immunohistochemical stains performed on the core biopsy revealed the infiltrate to be positive for EBV EBER, CD45 (dim), CD43, CD3 (partial, dim), CD2, CD7, CD4 (equivocal dim), and CD30 (rare dim, ~1%), and negative for PAX5, CD19, CD20, CD22, CD79a, CD8, and CD56. Flow cytometry showed a CD3+ CD4+ CD2+ CD7+ population lacking TCR g/d, TRBC1, CD5, CD57, and CD56, and essentially no B lineage events.

The patient's previously diagnosed DLBCL one year prior was positive for CD19, CD20, CD22 (50%), EBV EBER, CD30, BCL2, BCL6 (subset), MUM1, and MYC, and negative for CD3 and CD5.

Cytogenetics

Karyotype analysis showed a normal female karyotype.

Molecular Studies

Single cell RNA sequencing was negative for chimeric antigen receptor, with amplification of chromosome 1q and deletion of chromosome 6q. Further analyses are ongoing.

Proposed Diagnosis

EBV+ large T cell lymphoproliferative disorder following CART therapy for EBV+ diffuse large B cell lymphoma

Interesting Feature(s)

The United States Food and Drug Administration (FDA) is currently investigating confirmed reports of T cell malignancies arising in the setting of CAR T cell therapy. This case raises a differential diagnosis of transdifferentiation, evolution of an undiagnosed underlying follicular helper T cell lymphoma, or a de novo EBV+ HLH-related T lymphoproliferative disorder. Notably, the recurrent tumor was not chimeric antigen receptor positive, making a de novo CAR T cell-derived T cell lymphoma less likely. Transdifferentiation of B cell lymphomas to a T cell or histiocytic phenotype is a rare but established phenomenon, and it remains to be seen if CAR T therapy may predispose to such events, as some studies have suggested (see references).

References:

1. Laurent C, et al. Resistance of B-Cell Lymphomas to CAR T-Cell Therapy Is Associated With Genomic Tumor Changes Which Can Result in Transdifferentiation. Am J Surg Pathol. 2022 Jun 1;46(6):742-753.
2. Zhang Q, et al. Transdifferentiation of lymphoma into sarcoma associated with profound reprogramming of the epigenome. Blood. 2020 Oct 22;136(17):1980-1983.
3. Egan C, et al. The mutational landscape of histiocytic sarcoma associated with lymphoid malignancy. Mod Pathol. 2021 Feb;34(2):336-347.

EA4HP24-LYWS-262

Post-CD19-CAR-T therapy trans-differentiation of a transformed follicular lymphoma in to an undifferentiated malignant neoplasm of uncertain lineage.

Dr. Alireza Torabi[1], Dr. Jason Love[1], Dr. Angie Pham[3], Dr. David Wu[1], Dr. Kikkeri Naresh[2]

[1] University of Washington, Pathology/hematopathology, Seattle, USA; [2] Fred Hutch Cancer Center, Pathology/hematopathology, Seattle, USA; [3] CellNetix, Pathology Group, Seattle, USA

Case Description

This is a 52-year-old male who was diagnosed with a low-grade follicular lymphoma of left inguinal lymph node without evidence of large cell transformation and Ki-67 of 15 to 20%. However, bone marrow staging biopsy showed large B-cell lymphoma with a proliferative index of almost 100%. FISH showed IGH/BCL-2 translocation without evidence of MYC translocation (slides of these 2 cases not available). He was treated with 6 cycles of DA-EPOCH-R but PET/CT showed persistence of disease including hypermetabolic

adenopathy, osseous lesions and soft tissue masses. A CT-guided needle core biopsy of the right posterior chest wall mass confirmed an aggressive B-cell lymphoma, with Ki-67 of approximately 90% (detail below). He started salvage treatment with R-GemOx with quick improvement. However, follow-up MRI of the spine showed compression of the T4-T6 spinal cord, left paraspinal mass at the T4-T9, destructive mass involving the right fourth rib, multiple pleural-based masses, and extensive retroperitoneal adenopathy. He was started on dexamethasone followed by hyper-CVAD with bridge to CD19 CAR-T cell therapy (Yescarta). Following CART-therapy, PET/CT scan showed multiple bone and soft tissue lesions at the right iliac body/sacral ala, medial right 10th rib and left posterior seventh rib. Biopsies from right iliac lesion as well as bone marrow biopsy showed a poorly differentiated neoplasm without CD45 expression or any B-cell or T-cell markers (detail below). Shortly after, the patient passed away.

Biopsy Fixation Details

Formalin with decal.

Frozen Tissue Available

No.

Details of Microscopic Findings

Biopsy from right posterior chest wall lesion showed sheets of medium sized mononuclear cells, focally infiltrating into the skeletal muscle, with round nuclei, some with nuclear notch, fine chromatin, few with nucleoli, and sparse pink cytoplasm. Few scattered apoptotic bodies present, however, no overt starry sky noted.

Biopsy from the right iliac lesion also showed a primitive small round blue cell tumor.

Bone marrow biopsy showed small round blue cell tumor with foci of necrosis.

Immunophenotype

The tumor cells of the right chest wall mass were positive for CD20 (strong), BCL2, CD10, BCL6 (40%, weak to moderate), TdT, P53 (diffuse and strong), MUM1 (50%), and c-MYC (15-20%) and negative for CD34, SOX11, Cyclin D1, and CD30. Ki67 shows proliferation index of 80-90%. EBER ISH is negative.

Tumor cells in the bone marrow biopsy as well as iliac bone lesion were positive for CD56 and P53 and negative for any B cell markers (PAX5, CD79a, CD20, and CD19), OCT2, BOB1, CD3, CD45, CD34, OSCAR, AE1/AE3 synaptophysin or TTF-1. The neoplastic cells were not identified by flow cytometry.

Cytogenetics

Cytogenetic from right chest wall mass: Positive for IGH/BCL2 t(14;18) as well as positive for gains of 3q, 8q, and 14q. No evidence of structural gene rearrangements involving BCL6 or MYC.

FISH was POSITIVE for Bcl2 translocation on iliac bone lesion.

Molecular Studies

Chest wall mass lesion NGS positive for TP53, KMT2Dx2 , TNFRSF14, BCL2, NOTCH1, EP300, PHF6.

Iliac bone lesion NGS positive for TP53, KMT2Dx2, TNFRSF14, BCL2, KMT2D, DNMT3Ax2. Clonality for B-cell Ig gene rearrangement showed similar IGK clone without IGH.

Proposed Diagnosis

Lymphoblastic transformation of low-grade follicular lymphoma with trans-differentiation to undifferentiated malignant neoplasm of uncertain lineage.

Interesting Feature(s)

A low-grade mature B-cell follicular lymphoma gradual differentiation into blastic and then undifferentiated malignancy following CART-therapy.

EA4HP24-LYWS-26

Chronic lymphocytic leukemia with pseudo-Richter transformation consistent with recent interruption of ibrutinib

PhD/MD Pedro Farinha

BC Cancer, Pathology, Vancouver, Canada

Case Description

72-year-old woman with history of chronic lymphocytic leukemia (CLL) (2013) with 13q14.3 deletion by FISH (2021) and on ibrutinib since 2021, due to cytopenias. In March 2022, she was diagnosed with a right cheek lentigo maligna melanoma and had it completely resected with negative sentinel lymph nodes. In March 2023, she noticed a right neck mass (PET-avid, SUV max 10.7) with core biopsy showing in transit metastatic melanoma. A right neck lymph node dissection (levels 1 to 4) was performed in August 2023 (submitted specimen). Ibrutinib was on hold few days prior to neck surgery.The melanoma relapsed on the surgical scar that was re-excised on November 10th, 2023. Her last follow-up was on November 28th, 2023, with no systemic symptoms or enlarging lymph nodes/masses.

Biopsy Fixation Details

Buffered neutral formalin, 10%.

Frozen Tissue Available

No.

Details of Microscopic Findings

Metastatic melanoma was identified in 2 of the 44 isolated lymph nodes. All excised lymph nodes showed similar morphologic features with variably enlarged lymph nodes with almost complete effacement of the architecture by an atypical lymphoid infiltrate with a diffuse and vaguely nodular pattern. The nodules were pale, with variable small to large sizes, some suggesting proliferation centers (PC) with frequent coalescence. The infiltrate was composed almost entirely of sheets of medium to predominant large sized atypical cells with immunoblastic features. They were focally admixed with rare but still present small mature-looking CLL-like cells. In many areas, the large cells formed sheets suggestive of transformation into diffuse large B-cell lymphoma (DLBCL). The large cell aggregates were surrounded by reactive-looking lymphocytes.

Immunophenotype
All atypical cells, small to abundant large cells, were B-cells showing uniform expression of CD20, PAX5 (dimer in the larger cells), BCL2, CD5, CD23 as well as variable MUM1 and MYC (larger cells). These cells were negative for CD10, BCL6, cyclin D1 and significant TP53. EBV EBER ISH was also negative. The small lymphocytes were predominantly CD3+ T-cells. The proliferation rate (Ki67) was high in the atypical cells, approximately 90%, and highlighted the sheets of large cells.
Cytogenetics
Not done.
Molecular Studies
Note done.
Proposed Diagnosis
Chronic lymphocytic leukemia with pseudo-Richter transformation consistent with recent interruption of ibrutinib.
Interesting Feature(s)
The lymph nodes show morphology and phenotypic features consistent with transformation of CLL into DLBCL. Yet, these features, pseudo-Richter transformation (RT), have been described in CLL patients with recent interruption of ibrutinib.
This case highlights the diagnostic challenge and pitfall of RT in patients who develop disease progression while ibrutinib is temporarily interrupted. Caution should be taken to distinguish pseudo-transformation from true RT in the era of targeted therapy. While true RT requires aggressive immunochemotherapy, pseudo-transformation may be simply and effectively treated by resuming ibrutinib therapy. In these cases, after resumption of therapy, all the aggressive cytological features resolve/regress to “classical” CLL-like morphology.

EA4HP24-LYWS-226

Dasatinib-associated lymphadenopathy

Dr. Masoud Movassaghi, Dr. Yaping Ju, Dr. Endi Wang, **Dr. Imran Siddiqi**

Keck School of Medicine of USC (University of Southern California), Pathology Department/Hematopathology Division, Los Angeles, USA

Case Description
A 58-year-old female, diagnosed with chronic myeloid leukemia (CML) in 2018 and currently on dasatinib, presented with left axillary lymphadenopathy. An excisional biopsy was performed for diagnosis.
Biopsy Fixation Details
10% neutral buffered formalin
Frozen Tissue Available
N/A

Details of Microscopic Findings

H&E-stained sections reveal an enlarged lymph node. The majority of the lymph node is affected by a proliferation of lymphoid follicles that are expansile, closely spaced, and display marked variation in size and shape. Many of these follicles contain hyperplastic germinal centers. There is follicular lysis and varying degrees of progressive transformation of germinal centers (PTGC). Interfollicular zones primarily consist of small lymphocytes with frequent scattered eosinophils and plasma cells, along with rare immunoblasts. Notably, a separate discrete area of the lymph node, demarcated from the hyperplastic follicles, demonstrates a diffuse polymorphous cellular proliferation. This area comprises a heterogeneous admixture of small lymphocytes, loose clusters of epithelioid histiocytes (including a few scattered multinucleated giant cells), scattered eosinophils and plasma cells, and a few scattered immunoblasts, all in a background of increased vascularity. No diagnostic Reed-Sternberg cells or other overt cytologic atypia are identified.

Immunophenotype

Immunohistochemistry reveals numerous CD3-positive small T-cells in interfollicular zones and the polymorphous proliferation. Hyperplastic follicles concentrate CD20-positive B-cells, while additional stains exhibit CD4, CD8, and PD1 expression in T-cells, along with high Ki67 proliferation in germinal centers and the polymorphous proliferation. Notably, there is an absence of aberrant T and B cells. EBER (ISH) highlights few scattered large lymphocytes in interfollicular zones and the polymorphous proliferation. Flow cytometry shows no immunophenotypic evidence of a lymphoproliferative disorder.

Cytogenetics

N/A

Molecular Studies

- Positive for T-cell Receptor Gamma Gene Rearrangement
- Negative for T-cell Receptor Beta Gene Rearrangement
- Negative for B-cell Gene Rearrangement

Proposed Diagnosis

Dasatinib-associated lymphadenopathy

Interesting Feature(s)

The pattern of follicular hyperplasia observed in much of this lymph node, including markedly hyperplastic, closely-spaced, and irregularly-shaped lymphoid follicles with follicular lysis, progressive transformation of germinal centers, and rare EBV-positive cells, has been described in the setting of dasatinib-associated lymphadenopathy. While the overall findings are not diagnostic of lymphoma, the presence of the atypical polymorphous proliferation and clonal T-cell receptor gamma gene rearrangement is notable. Dasatinib-associated lymphadenopathy can rarely progress to lymphoma. Accordingly, correlation with clinical and radiographic findings and follow-up evaluation is recommended.

Cases Discussed by the Panel

EA4HP24-LYWS-17	ALK- ALCL in the setting of ibrutinib-treated CLL: a collision or a consequence?
EA4HP24-LYWS-18	PET+ generalized lymphadenopathy due to follicular hyperplasia with light chain-restricted germinal centers and extrafollicular activation of B-blasts after mRNA-1273 COVD-19 vaccination
EA4HP24-LYWS-23	Development of a follicular T-helper-cell lymphoma after therapeutic intervention with an anti-EGFR TKI (ocemertinib) for lung adenocarcinoma.
EA4HP24-LYWS-32	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) following Doxazocin and Bendroflumethiazide Administration
EA4HP24-LYWS-61	CNS polymorphic B cell lymphoproliferative disorder, EBV positive, in the setting of HIV, resolving with antiretroviral treatment
EA4HP24-LYWS-72	Atypical B-cell proliferation in the endometrium mimicking small B cell lymphoma
EA4HP24-LYWS-85	Reactive Lymphadenopathy Mimicking Large B Cell Lymphoma in a COVID-19 Vaccine Recipient
EA4HP24-LYWS-86	Drug induced lymphadenopathy：A highly mimic malignant case based on clinical information
EA4HP24-LYWS-87	Large atypical lymphoid cells EBER positive in a patient with ulcerative colitis
EA4HP24-LYWS-88	B-lymphoblastic leukemia (B-ALL) with atypical infiltrate after CAR T-Cell therapy
EA4HP24-LYWS-90	“Pseudo-Richter Transformation” following cessation of BTK-inhibitor therapy”.
EA4HP24-LYWS-93	CAR-T Complications
EA4HP24-LYWS-97	Early histological large cell change (pseudo-Richter transformation) in patient with B-CLL/SLL with ibrutinib treatment interruption for unrelated surgery – incidental finding and diagnostic pitfall
EA4HP24-LYWS-107	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Lymphadenopathy
EA4HP24-LYWS-124	Two distinct lymphomas in a patient with long-standing iatrogenic immune suppression for Crohn’s disease
EA4HP24-LYWS-138	Pattern approach of lympadenomegalia of HIV-positive patient
EA4HP24-LYWS-149	Eosinophil-enriched lymphadenitis, most consistent with DRESS, in a post COVID-19 vaccination
EA4HP24-LYWS-173	An EBV+ polymorphic lymphoproliferative disorder arising in the setting of iatrogenic immunosuppression (chemotherapy/radiation therapy)
EA4HP24-LYWS-186	Therapeutically Tenacious T cells: Accelerating CARs Parking in the CNS and GI
EA4HP24-LYWS-188	Cervical lymphadenopathy in a patient on dasatinib and bosutinib

EA4HP24-LYWS-203	DRESS Syndrome
EA4HP24-LYWS-218	Pseudo-Richter Transformation in the Setting of Presurgical Zanubrutinib Therapy Interruption in a Patient with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
EA4HP24-LYWS-221	Pseudo-Richter Transformation in An Otherwise Clinically Silent Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Patient Following Temporal Acalabrutinib Interruption
EA4HP24-LYWS-234	Extranodal marginal zone lymphoma in the setting of methotrexate therapy
EA4HP24-LYWS-280	Extranodal diffuse large B-cell lymphoma in a child with a primary atopic disorder and a germline *PTPN13* variant receiving immunomodulatory therapy.
EA4HP24-LYWS-286	Subcutaneous panniculitis-like T-cell lymphoma post immunotherapy
EA4HP24-LYWS-291	Dasatinib-associated lymphadenopathy in a patient with chronic myeloid leukaemia
EA4HP24-LYWS-297	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: Cutaneous and lymph node findings
EA4HP24-LYWS-321	PTEN-related T-cell lymphoproliferative disease under chronic iatrogenic mTOR inhibition
EA4HP24-LYWS-323	Epstein-Barr Virus Positive Iatrogenic Lymphoproliferative Disorder in a Patient with Chronic Refractory Immune Thrombocytopenic Purpura Receiving Immunomodulatory Therapies
EA4HP24-LYWS-330	Infectious mononucleosis complicated with spontaneous splenic rupture and a clonal CD8+ T-cell lymphoproliferation mimicking a T-cell lymphoma.
EA4HP24-LYWS-359	EBV(+) large B-cell lymphoma of the brain in the setting of immuno-suppressive medication
EA4HP24-LYWS-363	Diffuse Large B-cell Lymphoma Associated with Chronic Inflammation
EA4HP24-LYWS-375	EBV-positive B-cell lymphoproliferation in mesenteric lymph nodes of a patient with colorectal adenocarcinoma pretreated with anti-PD1 (Pembrolizumab)
EA4HP24-LYWS-384	Post-COVID Vaccine Induced Lymphademnopaty
EA4HP24-LYWS-388	A transformed lymphoma or another lymphoma associated with IDD?
EA4HP24-LYWS-409	T-lymphoblastic lymphoma/leukemia in the setting of germline SMARCA4 mutation, prior cytotoxic chemotherapy and EZH2 inhibitor.
EA4HP24-LYWS-453	Polymorphic lymphoproliferative disorder, EBV-positive in the context of iatrogenic immunosupression
EA4HP24-LYWS-473	Atypical PD1+ CD8 cell proliferation after the treatment of Everolimus and a relative remote exposure to Pembrolizumab

EA4HP24-LYWS-474	Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma involving the liver, in the setting of autoimmune hepatitis treated with azathioprine

EA4HP24-LYWS-17

ALK- ALCL in the setting of ibrutinib-treated CLL: a collision or a consequence?

Prof. Alexandar Tzankov, Dr. Magdalena Brune

University Hospital Basel, Pathology, Basel, Switzerland

Case Description

M, 70

History of CLL since 2016

- 4/2018-9/2018: 6x bendamustine + rituximab -> PR
- 8/2019: progression -> ibrutinib 8/2019-6/2023 -> CR (5/2023)
- 6/2023: worsening with fever and dyspnea, radiologically suspect of Richter's transformation (PET+ tumorous mass obstructing the left bronchus), while still being on ibrutinib (submitted specimen)

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

Transbronchial biopsy with interstitial infiltration of the lung parenchyma by highly apoptotic and mitotically active discohesive blastoid cells with some epitehlioid cytomorphology, and with larger areas of diffuse, destructive infiltrates by the same blastoid cells.

Immunophenotype

Positivity for: CD2, dimCD3, CD7, CD8 (paritial but string), CD30, granzyme B, TIA1, TCRβ-F1
Negativity for: ALK, CD4, CD5, CD19, CD20, CD22, CD23, CD79a, EBER, TCRδ, LEF1, perforin, PAX5. RORγt

Cytogenetics

CLL initially 15, dup(17q), del(18q), del(21q), acquired CN-LOH 17p in 2021
ALCL not karytotypized

Molecular Studies

IGHV unmutated
initially *TP53* w.t., acquired *TP53* mutation in 2021

Proposed Diagnosis

ALK-negative anaplastic large T-cell lymphoma

Interesting Feature(s)

The case on the one hand underscores once more the value of lesional biopsies to verify the diagnosis and falsify differnetial dieagnoses in clinically or radiologically suspected Richter's transformations, on the other hand - and being our second case* of a CLL-

patient developing a T-cell lymphoma under ibrutinib - it raises the question of coincidence or causality.

Generally, there is evidence for interference of ibrutinib with T-cell functions, as ibrutinib:

- inhibits Tec-family kinases such as IL2–inducible kinase (ITK), a proximal member of the TCR-signaling cascade
- alters T-cell functions in CLL:
  - expansion of memory T-cells, Th1 polarization, reduced expression of inhibitory receptors
  - improved immune synapse formation between T-cells and CLL cells
- increases the risk of infections (i.e., aspergillosis) that maybe due to inhibition of ITK in T-cellsWhether these effects of ibrutinib may have played a role or whether ibrutinib generally increases the risk of developing T-cell lymphoma in respectively treated individuals remains to be determined, but hematopathologists should become aware of this poorly documented but possible side effect of it.

References:

- Lionakis et al (2017). Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell. 31, 833–843 e5.
- Long et al. (2017). Ibrutinib treatment improves T cell number and function in CLL patients. J. Clin. Invest. 127, 3052–3064.
- Ghez et al. (2018). Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood. 131,:1955–1959.
- Flinsenberg et al. (2019). Differential effects of BTK inhibitors ibrutinib and zanubrutinib on NK cell effector function in patients with mantle cell lymphoma. Haematologica 105, e76–e79.
- Mhibik et al. (2019). Harnessing the Effects of BTKi on T Cells for Effective Immunotherapy against CLL. Int. J. Mol. Sci. 21:68.
- *Pillonel et al. (2020). Routine next generation sequencing of lymphoid malignancies: clinical utility and challenges from a 3-Year practical experience. Leuk Lymphoma. 61, 2568-2583.
- Gu et al. (2021). Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol. 14, 40.

EA4HP24-LYWS-18

PET+ generalized lymphadenopathy due to follicular hyperplasia with light chain-restricted germinal centers and extrafollicular activation of B-blasts after mRNA-1273 COVD-19 vaccination

Prof. Alexandar Tzankov, Dr. Magdalena Brune

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Case Description

M, 28 with a history of scrotal abscess in 2013, efficiently eradicated HP+ gastritis in 2020, COVID-19 in January 2021, ureterolithiasis in June 2021, and COVID-19 mRNA-1273 vaccination in October 2021 developed a generalized PET+ lymphadenopathy and splenomegaly with high clinical suspicion of lymphoma in November 2021.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

Diagnostic lymphadenectomy of the largest and most PET-avid, left-axillary lymph node reveals follicular hyperplasia (FH) and extrafollicularly activated B-blasts.

Immunophenotype

The B- and T-zonation of the lymph node is well preserved The germinal centers are hyperproliferative and show a retained dark zone/pale zone pattern as well as BCL2-negativity. Most germial centers show lambda light chain-restriction, while one appears kappa light chain-restricted.

Cytogenetics

n.a.

Molecular Studies

n.a.

Proposed Diagnosis

Reactive adenopathy (LA) with light chain-restricted germinal centers and extrafollicular activation of B-blasts most likely due to mRNA-1273 COVD-19 vaccination

Interesting Feature(s)

COVID-19 vaccination-induced LA are among the most common vaccine side effects[ç], and are tightly linked to mRNA-1273[$]. This case shows rather very severe clinical presentation with generalized LA and splenomegaly mimicking lymphoma but rather characteristic morphologic patterns hematopathologists should be aware of:

- light chain-restricted germinal centers as described by Patil et al.*
- extrafollicular activation of B-blasts as described by Tzankov[&] and Menter et al.[#]Vaccination-induced LA likely reflect disordered immune response[#] the evince for

which is followingly discussed: 1) a common pattern observed is the so called extrafollicular activation of B-blasts that usually generates short lived plasma cells without immunoglobulin class switch"; 2) on gene expression profiling, they cluster apart from COVID-19 LA and FH, but overlap with extrafollicular activation of B-blasts and hemophagocytic lymphohistiocytosis; 3) they contain less memory and more naïve B-cells compared to unremarkable lymph nodes, infectious mononucleosis, FH and COVID-19 draining pulmonary lymph nodes of lethal COVID-19; 5) and they overexpress *TLR10* (opposite to other TLRs, TLR10-mediated signaling does not activate the immune system and shows immunosuppressive effects).[#] 6) Clinically, mRNA vaccine-induced LA more commonly occur in females, individuals with known immune deregulation, and cancer. With resepct to the latter, they may vice versa mimic lymphoma or metastatic disease clinically, radiologically and even at the microscopic level. Both the clinico-radilogical context and especially the histological patterns of vaccination-induced LA thus represent serious potential diagnostic pitfalls hematopathologists should be aware of.

Referneces:

- [ç]N Engl J Med 2021,385:1078
- [$]J Med Virol 2022,94:1833
- *Virchows Arch 2023,482:905;
- [&]Clin Case Rep 2022,10:e05398
- [#]Front Immunol 2023,14:1285168
- "Histopathology 2005,47:90

EA4HP24-LYWS-23

Development of a follicular T-helper-cell lymphoma after therapeutic intervention with an anti-EGFR TKI (ocemertinib) for lung adenocarcinoma.

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Case Description

A 75 year old female developed a lung adenocarcinoma in 2014. She was treated with a VATS lingulectomy and wedge resection left lower lobe + adjuvant chemotherapy (cisplatine/gemcitabine). In 2019 she developed a recurrent adenocarcinoma, as well as metastatic brain lesions. Since an activating mutation in exon 18 (p.Gly719Cys c.2155G>T)

and in exon 20 (p.Ser768Ile c.2303G>T) of the EGFR gene was detected in the lungtumor, she was treated with a 3rd generation EGFR-TKI Osimertinib, in compassionate use. Three years later she developed multiple supra- and infradiafragmatic lymphadenopathies, suspicious for malignancy (quid metastatic disease?) and a lymph node biopsy was performed (provided as LYWS-23).

Biopsy Fixation Details

FFPE

Frozen Tissue Available

available

Details of Microscopic Findings

Lymph node with architectural effacement due to a diffusely growing population of medium-sized atypical lymphocytes with irregular nuclear contours and hyperchromatic to vesicularly enlarged nuclei with recognizable eosinophylic nucleoli. The cytoplasm shows clear-cell differentiation. The background contains numerous eosinophils. Scattered high endothelial venules are observed.

Immunophenotype

The atypical lymphoid population is

•Positive for CD3, CD2, CD5, PD1, ICOS, IMP3, TCRbetaF1

•Partially positive for CD30, CD4

•Negative for PAX5, CD20, CD10, BCL-6, cytotoxic markers, NCAM/CD56, CD57, CD8, CD7, CXCL13, CD21 (no FDC proliferation), EBER (only focal sparse + cells)

Cytogenetics

•Polyclonal result for BCR

•Monoclonal result for TCR:•TCRB: monoclonal (265); TCRG: monoclonal (135-254)

Very complex hypodiploid karyotype: 45,X,-X,del(2)(q32q34),inv(4)(p11q26),t(4;13)(p13;q11),der(5)t(5;10)(q14;q22),del(6)(q16q22),+7,add(9)(p21),-10,add(12)(q13),del(14)(q11q?23),del(16)(q21q23),der(17)t(17;17)(p12;q11),-21,+mar[9]

Molecular Studies

•NGS: no aberrations supporting clonal hematopoiesis; No variants recurrent in TFH lymphoma (RHOA, TET2, IDH2, DNMT3A, CD28)

•VUS class III: GNA13_exon4 c.867C>G,p.(Phe289Leu)

Proposed Diagnosis

Lymphoma associated with therapeutic intervention (chemotherapy + anti-EGRF-TKI): Subtype: T-follicular helper cell lymphoma, but lacking the recurrent molecular variants ((RHOA, TET2, IDH2, DNMT3A, CD28)

Interesting Feature(s)

•Development of lymphoma as a secondary malignancy after therapeutic intervention with a anti-EGFR TKI for lung adenocarcinoma

•Immunophenotype of TFH lymphoma, but lacking the known recurrent molecular variants

•Detection of variant GNA13 (Guanine Nucleotide Binding Protein (G Protein), Alpha 13): VUS class III:

+ most frequently mutated gene in germinal center (GC)-derived B-cell lymphomas, including nearly a quarter of Burkitt lymphoma and GC-derived diffuse large B-cell

lymphoma.
+ potent tumor suppressor gene; https://doi.org/10.1182/blood-2015-07-659938
+ Mechanistically, Gα13-RhoA-ROCK2 axis is responsible for the Tfh cell differentiation from naïve precursors: role in development of TFH lymphoma?
•No association with EBV
•IMP3 expression in T-cell lymphoma is not well studied:
+ IMP-3 is a member of the insulin-like growth factor II mRNA binding protein (IMP) family of proteins
+ IMP3 is expressed in lymphoma types, mainly of GC B-cell origin and Hodgkin (PMID: 19698973)
+ IMP3 expression in CD30+ PTCL, NOS (https://doi.org/10.3324/haematol.2012.081935)

EA4HP24-LYWS-32

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) following Doxazocin and Bendroflumethiazide Administration

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Case Description

A 77-year-old female was referred in mid October 2023 with progressive lethargy, fever (up to 38.7^{0}C) and a three-week history of a generalised rash. She had a history of dyslipidaemia, controlled with atorvastatin (20mg daily), and hypertension regulated with perindopril 4mg (1 - 0 - 2) and atenolol (50mg daily). Following sustained elevated blood pressure readings, she was started on bendroflumethiazide (5mg daily) in early September and, two weeks after, doxazocin (4mg twice daily). The rash started approximately a week after initiation of doxazocin. On examination, she had multiple infiltrated erythematous scaly plaques, predominantly involving the face, all four limbs and, to a lesser extent, the trunk. No lymphadenopathy or organomegaly was noted. Her parameters were unremarkable and she was afebrile at presentation.
Blood investigations showed a total white cell count of 16.8x10^9/L, with neutrophilia (10.5x10^9/L), eosinophilia (3.8x10^9/L) and normocytic normochromic anaemia (haemoglobin of 10.7g/L with a MCV of 87.5fL and a MCHC of 32pg). Lymphocyte, monocyte, basophil and platelet counts were within normal range. A blood film confirmed eosinophilia, showed red cell poikilocytosis with echinocytes and elliptocytes and a left shift in granulocytic maturation. Coagulation studies were normal. CRP levels were elevated at 119.8 mg/L. Renal function was deranged, with a urea of 10.4 mmol/L, a serum creatinine of 144 µmol/L and hyponatraemia at 121mmol/L. Liver function was also impaired, with a bilirubin level of 44.6 µmol/L, ALP of 232 U/L, γGT of 271 U/L and ALT of 100

U/L. A hepatic panel excluded viral and autoimmune aetiologies. A full septic screen was negative.
Bendroflumethiazide was withdrawn in view of hyponatraemia however, she failed to improve biochemically and the rash persisted. A skin punch biopsy taken a few days into admission supported a drug-associated aetiology. Given that her symptoms started shortly after initiation of doxazosin, the latter was withdrawn and prednisolone was initiated at 40mg daily, tailing down at 5mg intervals every five days. She clinically improved, with resolution of the rash and normalisation of haematological and biochemical values three weeks of cessation of doxazocin.

Biopsy Fixation Details

The skin biopsy was preserved in 10% neutral-buffered formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

The skin punch biopsy showed a perivascular and, to a lesser extent, interstitial inflammatory infiltrate comprised of lymphocytes, histiocytes and eosinophils in the upper and mid-dermis. Focal lymphocyte exocytosis into the epidermis with mild associated spongiosis and subtle overlying parakeratosis was appreciated. Eosinophilic spongiosis was not evident.

Immunophenotype

N/A

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Drug-associated eruption with eosinophilia and systemic symptoms (DRESS), likely secondary to doxazosin, bendroflumethiazide or combination therapy.

Interesting Feature(s)

DRESS has been classically associated with anticonvulsants (phenytoin, carbamazepine and phenobarbital), antimicrobials (sulfonamides, β-lactams, vancomycin, anti-tuberculosis agents and antiretrovirals), NSAIDs, dapsone, hydroxycholoquine and allopurinol. In this case, while doxazosin was favoured as the culprit medication, given that it was introduced last, it cannot be entirely excluded that either bendroflumethiazide alone or a combination of the two agents accounted for DRESS. Irrespectively, neither of these two medications are documented as classical agents, highlighting a unique aspect of this case.

EA4HP24-LYWS-61

CNS polymorphic B cell lymphoproliferative disorder, EBV positive, in the setting of HIV, resolving with antiretroviral treatment

Dr. Danielle Even Fridrich, Dr. Shachar Naor, Dr. Ginette Schiby

sheba medical ceneter, pathology, Ramat Gan, Israel

Case Description·Male, 30 years old.
·Diagnosed with HIV 4 months prior to presentation, CD4 count of 43 CD4/mm3 at presentation.
·Presented with progressive mental and cognitive decline in the past month, weight loss and daily fever spikes up to 39.5°C.
·MRI showed necrotic lesions in the right temporal lobe and the left occipital lobe with peripheral enhancement along with vesogenic edema in the proximity. In addition: hyperintense infiltrating changes in periventricular white matter, corpus callosum and the basal ganglia on the right side.
·PET-CT: no lymph node or spleen involvement.
·EBV PCR in the blood was 3*103 cp/ml.
·A core needle biopsy from the occipital lesions was performed.
·EBV PCR on the fresh brain tissue was positive.

Biopsy Fixation Details

Formalin fixed

Frozen Tissue Available

None

Details of Microscopic Findings

The brain tissue shows sheets of necrotic cells. Other areas are composed of histiocytes and a polymorphous lymphoid population including small and medium sized lymphocytes as well as large cells with delicate nucleoli.

Immunophenotype

The CD20 highlighted sheets of necrotic cells, partly in a perivascular distribution. The CD3 showed scattered small T cells. The CD68 was positive in numerous histiocytes. The CD30 was negative.
Stains for microorganisms (PAS and GMS stains) as well as immunostains for CMV, HHV8 and Toxoplasma were negative.
Immunostains for nuclear antigens including PAX5, MUM1, BCL6, c-MYC and Ki67 were non-contributory due to the necrosis.
The ISH-EBER was positive in a few cells in the viable areas and non-contributory in the necrotic areas.

Cytogenetics

The tissue was almost completely exhausted

Only 40 cells were counted and none of them showed rearrangement of BCL6, BCL2 or c-MYC

Molecular Studies

Monoclonal IgH and IgK rearrangements

Proposed Diagnosis

CNS Polymorphic monoclonal B-LPD, EBV positive, in the setting of acquired immunodeficiency (HIV)

Interesting Feature(s)

- The differential with EBV positive DLBCL (primary CNS lymphoma) was challenging in this case, especially with the extensive necrosis and the clonality. Even with the polymorphic infiltrate one could argue that the findings might be consistent with the polymorphic variant of EBV positive DLBCL.
- Since the patient's neurological clinical status was rapidly deteriorating the clinicians were inclined to treat aggressively with chemotherapy or at least Rituximab. However since no clear sheets of large cells could be identified and the tissue was scant we hesitated to call this process DLBCL, and fortunately in the meanwhile he began receiving ART and his neurological symptoms have shown some improvement. After discussion with the clinicians a decision to wait and watch was made and indeed the patient eventually recovered completely both symptomatically and radiologically (on repeat MRI).
- Another differential diagnosis that would have been considered if the patient was not immunosuppressed was Lymphomatoid Granulomatosis. However the diagnosis of LyG should not be made in patients with immunodeficiency.
- This case shows the importance of accurately "calling" the process and convey the histologic findings to the clinicians so a decision can be made regarding appropriate treatment. Do not overcall DLBCL in these cases, especially if that would mean aggressive chemotherapy treatment.
- Even cases with extensive necrosis that may seem "alarming" might improve in these patients following reversal of the immunodeficiency state (i.e. ART in the case of HIV).

EA4HP24-LYWS-72

Atypical B-cell proliferation in the endometrium mimicking small B cell lymphoma

Dr. Siok-Bian Ng[1,2], Dr. Diana G.S. Lim[2]

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Case Description

A 46-yr-old woman complained of dyspareunia. Intrauterine device (IUD) was inserted 2 years ago in Aug 2021. No other history of note.

Ultrasound of uterus, ovaries and fallopian tubes is normal.

Endometrial sampling showed atypical B-cell proliferation.

Patient is well and declined further investigations

Biopsy Fixation Details

Specimen was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Nil

Details of Microscopic Findings

• Diffuse monotonous infiltrate of lymphocytes associated with ulceration, acute and chronic inflammation and stromal breakdown.

• Lymphocytes are small with round or slightly irregular nuclei and indistinct nucleoli.

• Some lymphoid cells show moderate amount of cytoplasm, suggestive of monocytoid cells.

• No prominent plasmacytic differentiation.

• No reactive follicles or large cell proliferation

• No sclerosis

Immunophenotype

• The lymphoid population comprises a mixture of B and T cells with predominance of B cells.

• The B cells are positive for CD20 and CD79A. They do not show aberrant expression of CD5, CD10, cyclinD1, CD23 and CD43 (CD43/PAX5 double stain performed)

• Ki-67 proliferation index is low (10-20%)

• Plasma cells polytypic for kappa and lambda (in situ hybridisation)

• Absence of follicular dendritic cell meshworks (absence of staining for CD21 and CD23)

• CD3 and CD5 stain large number of reactive T cells

• EBER in situ hybridization negative

Cytogenetics

Nil

Molecular Studies

PCR for IgH/IgK gene rearrangement polyclonal

Proposed Diagnosis

Atypical B-cell proliferation associated with IUD, compatible with lymphoma-like lesion of the female genital tract

Interesting Feature(s)

1. Florid reactive lymphoid hyperplasia mimicking lymphoma can involve the cervix and less often the endometrium and vulva (lymphoma-like lesions – "LLL")
2. LLL may be associated with Epstein-Barr virus (EBV), Chlamydia trachomatis, HIV and HPV infection, intra-uterine devices, or occur following surgery
3. Clues to diagnosis:

- Superficial located, surface erosion/ulceration, aute inflammation and polymorphous infiltrate of small and large lymphoid cells, mixture of B and T cells, polytypic plasma cells
- Lack of mass lesion, large size, deep invasion, cellular monomorphism and prominent sclerosis

References:

1. Young RH, Harris NL, Scully RE. Lymphoma-like lesions of the lower female genital tract: a report of 16 cases. Int J Gynecol Pathol. 1985;4(4):289-99
2. Geyer JT, Ferry JA, Harris NL, et al. Florid reactive lymphoid hyperplasia of the lower female genital tract (lymphoma-like lesion): a benign condition that frequently harbors clonal immunoglobulin heavy chain gene rearrangements. Am J Surg Pathol. 2010 Feb;34(2):161-8
3. Ramalingam P, Zoroquiain P, Valbuena JR, Kemp BL, Medeiros LJ. Florid reactive lymphoid hyperplasia (lymphoma-like lesion) of the uterine cervix. Ann Diagn Pathol. 2012 Jan;16(1):21-8.

EA4HP24-LYWS-85

Reactive Lymphadenopathy Mimicking Large B Cell Lymphoma in a COVID-19 Vaccine Recipient

Dr. Merit Hanna

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Case Description

A 47-year-old New Zealand European female presented with widespread lymphadenopathy and palpable hepatosplenomegaly approximately two weeks after a third dose of the BioNTech mRNA COVID-19 vaccine. Clinical history revealed a transient febrile illness and gastrointestinal disturbance. Medical background included asymptomatic autoimmune thyroiditis. The patient was on no regular medication. Apart from palpable lymphadenopathy and hepatosplenomegaly, there were no other clinical findings.

Presenting complete blood count showed normocytic anaemia (HB 99 g/L, MCV 93 fL), neutrophilia (8.5 x 10^9/L), and lymphopenia (0.5 x 10^9/L).
Blood film examination showed rouleaux formation and pleomorphic lymphocytes, some with immature chromatin, discernible nucleoli and plasmacytoid morphology.
Biochemistry showed an elevated lactate dehydrogenase at 370 U/L, cholestatic deranged liver function (GGT 125 U/L, alkaline phosphatase 158 U/L, bilirubin 35 µmol/L).
Autoimmune screen and viral serology (hepatitis, HIV, CMV and EBV) were negative.
A staging CT scan showed extensive lymphadenopathy in the neck, chest, abdomen and pelvis, and splenomegaly measuring 155 mm.
She proceeded to have a righ axillary lymph node core biopsy and a bone marrow biopsy.
Despite investigations favouring a B cell neoplasm, the patient was clinically well and a decision to closely observe was made.
Three months later, a repeat staging scan and clinical examination showed a complete resolution of the lymphadenopathy and organomegaly.

Biopsy Fixation Details

Standard technique

Frozen Tissue Available

No

Details of Microscopic Findings

Core biopsy of the right axillary node showed effacement of normal nodal architecture with CD20 weakly positive and CD79a positive large lymphoid cells. The proliferative index based on Ki67 was 60%. They were mixed with small mature T lymphocytes. In addition, there were 20% polyclonal plasma cells.
The bone marrow aspirate showed increased lymphocytes (34%) with pleomorphic appearance, large cells with irregular nuclei and immature chromatin, as well as plasmacytoid lymphocytes. Plasma cells increased at 8%. The trephine biopsy showed increased CD20 positive B cells (50% of all cells) with interstitial, nodular, focal intertrabecular and paratrabecular distribution.

Immunophenotype

Flow cytometry analysis on the lymph node biopsy showed a population of B cells (52% of all lymphocytes) with variable CD20 expression, absent surface light chain expression, negative for CD5 and CD10, bright CD38 and a high Ki-67 of 63%.

Cytogenetics

FISH showed no *MYC*, *BCL2* or *BCL6* rearrangement.

Molecular Studies

PCR for IgH gene rearrangement showed a monoclonal pattern.

Proposed Diagnosis

Reactive lymphadenopathy post COVID-19 vaccine.

Interesting Feature(s)

There is significant lymphocyte populations in the lymph node and bone marrow, with abnormal immunophenotype by flow cytometry analysis and evidence of clonality by IgH gene rearrangement.
Whilst the morphological, histopathological, immunophenotypic and molecular features are consistent with a neoplastic/large B cell lymphoma, the clinical resolution of

lymphadenopathy without cytotoxic therapy is in keeping with a reactive process. This case highlights the limitations of flow cytometry in assessing clonality. Absent surface light chain expression can suggest clonality but reactive B cells can also down regulate surface Ig expression particularly in florid follicular hyperplasia. In this case the monoclonal pattern on PCR is likely a false positive due to preferential priming of VDJ arrangement, paucity of target cells, and/or focal clustering of clonally-related lymphocytes.

EA4HP24-LYWS-86

Drug induced lymphadenopathy：A highly mimic malignant case based on clinical information

Prof. Yu Li

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Case Description

A 40-year-old male with superficial lymph node enlargement in the neck, armpits, and groin for over a month, shortness of breath, and fatigue for 3 days.

Supplementary medical history: He was diagnosed with mandatory spondylitis in May 2020, and taking regular medication such as thalidomide, sulfasalazine, and traditional Chinese medicine (details unknown) in July 2020. His symptoms, signs, laboratory and imaging abnormalities appeared one month after taking the medication.

Laboratory examination: WBC 54.27×10^9/L, β2-MG ↑6.60 mg/L, LDH ↑1139.3U/L, WBC ↑54.27 ×10^9/L, β2-MG ↑6.60 mg/L, LDH ↑1139.3U/L, EBV VCA IgG ↑26.40 AU/ml; EBV VCA IgA↑9.91 AU/ml; EBV NA IgG >50.00 AU/ml. Blood mature lymphocytes 52%, abnormal lymphocytes 6%, monocytes 28%, eosinophils 6%, neutrophils 8%. Bone marrow(BW)/peripheral blood(PB) morphology suggests that immature lymphocytes in BM account for 16.5%, while immature lymphocytes in PB account for 22%. CT shows splenomegaly, multiple enlarged lymph nodes in the retroperitoneum, hepatic hilum, and mesenteric area and large amount of pleural effusion on the right side.

Biopsy Fixation Details

10% Neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The structure of lymph nodes is damaged without visible follicular structure. Scattered large lymphoid cells are distributed, large cells are round or oval in shape, with one or more nucleoli visible, some nucleoli centered, and a starry sky phenomenon can be seen. Large cells showed B lineages of differentiation at different stages.

Immunophenotype

Positive: CD20 and PAX-5 (partially, large cells varies), CD30 (varies), CD2, CD3, CD5, CD7, CD4> CD8, GrB, Ki-67 (70%+).

Negative: CD21, TIA-1,CD56

Cytogenetics

Not done.

Molecular Studies

In situ hybridization: Epstein-Barr virus receptor in situ hybridization: negative

Molecular Analysis: IgH(-), Igκ(-), IgL(-); TCRβ (-), TCRγ (-), TCRδ (-).

Proposed Diagnosis

Drug induced lymphadenopathy, characterized by paracortical region lymphoid tissue proliferation and cytotoxic phenotype characteristics

Interesting Feature(s)

Drug-induced hypersensitivity syndrome (DiHS) is often caused by drugs such as carbamazepine, dapsone, and allopurinol in clinical practice. Sulfasalazine is a commonly used medication for the treatment of ulcerative colitis and rheumatoid arthritis. DiHS induced by sulfasalazine is very rare and has gradually been recognized and valued in recent years. DiHS induced by sulfasalazine is very similar to infectious mononucleosis (IM) in clinical practice, often manifested as fever, rash, lymph node enlargement, and hepatosplenomegaly. Laboratory tests have shown a significant increase in PB abnormal lymphocytes and abnormal liver function. Clinically, it is easy to misdiagnose as lymphoma. Our case also showed malignancy in clinical laboratory tests, although some large cells were visible in morphology, it still showed B lineages of differentiation at different stages, with varying expression of CD30, and gene rearrangement showed negative results for both B and T lineages.

Differential Diagnosis: IM and cytotoxic T-cell lymphoma (literature reports suggest that carbamazepine can induce CD30+T-cell lymphoma)

Follow-up: After stopped treatment with thalidomide, sulfasalazine, and traditional Chinese medicine in September 2020 , and changed to supportive treatment, the symptoms and signs (enlarged liver and spleen, superficial body, and large lymph nodes in the abdominal cavity) gradually subside, and laboratory tests and imaging examinations gradually return to normal. Followed up for 21 months, no abnormalities were found after re-examination.

EA4HP24-LYWS-87

Large atypical lymphoid cells EBER positive in a patient with ulcerative colitis

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Case Description

21-year-old male patient, diagnosed 2 years ago with ulcerative colitis, with poor response to multiple treatments (mesalazine, infliximab and tofacinib). At the time of the biopsy, he was treated with corticosteroids and vedolizumab. Consulted for severe rectal bleeding and anemia, without lymphadenopathy, organomegaly or LDH elevation. A colonoscopy was performed in which severe disease activity with significant ulceration was identified, therefore requiring a subtotal colectomy.

Biopsy Fixation Details

The biopsy material was fixed in 10% formalin and embedded in paraffin following routine histological tissue processing.

Frozen Tissue Available

No

Details of Microscopic Findings

Colonic and ileal mucosa show extensive ulceration with alteration of the architectural pattern and loss of mucosecretion. A severe inflammatory component of a polymorphous lymphoid infiltrate with full range of maturation including small B cells, plasma cells, immunoblasts and large atypical cells, admixed with a variable number of reactive T cells was observed. In the ulcerated zones, the inflammatory component is interspersed with granulation tissue and epithelial cells with regenerative changes.

Immunophenotype

The large atypical lymphoid cells were of B-cell phenotype CD45, CD20 and CD30 positive. The lymphoid infiltrate was diffusely positive for CD45, CD20 and CD79a, the plasma cells were CD138 and MUM-1 positive. CD3 and CD5 was positive in T cells with a rim image at the base of the ulcer. CD10 and BCL6 were negative. Proliferative index Ki-67: 70%. No restriction of light chains is observed (in situ hybridisation study).The "in situ" hybridisation for Epstein-Barr virus mRNA (EBERs) has been positive in both the large and small lymphoid cells.

Cytogenetics

Unrealized

Molecular Studies

IGH gene rearrangement was polyclonal. TCR gene rearrangement was unrealized.

Proposed Diagnosis

Multiple colon ulcers with severe ulcerative colitis and marked atypical plasmocellular inflammation associated with infection by Epstein Barr virus, compatible with

polymorphous lymphoproliferative disorder associated with Epstein Barr virus in the context of immune deficiency/dysregulation.

Interesting Feature(s)

Despite the presence of atypical cells, the clinical course was indolent, without progression to disseminated disease, after 14 months follow –up the patient remains in complete remission upon reduction of immunosuppression.

The biopsy shows ulcers that mimick an EBV+ mucocutaneous ulcer, with prominent rim of small T- lymphocytes CD3 and CD5 at the base. In our case with more than two GI lesions, the term EBV+ polymorphic B cell LPD is more appropriate.

EA4HP24-LYWS-88

B-lymphoblastic leukemia (B-ALL) with atypical infiltrate after CAR T-Cell therapy

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Case Description

An 8-year-old femalepresented with B-ALL with a normal karyotype, homozygous *CDNK2A/B* loss, loss of one copy of *ETV6*, and somatic trisomy 21 noted on FISH studies. She was originally treated with Children's Oncology Group (COG) AALL0932 protocol, relapsed multiple times over two years, and was re-treated per the AALL1331 protocol followed by a matched sibling bone marrow transplant. She relapsed again three months post-transplant, at which point a next generation sequencing (NGS)-based mutation panel showed an *NRAS* G12S mutation. She received three doses of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy Kymriah/Tisagenlecleucel followed by a second unrelated bone marrow transplant but remained MRD-positive and developed extramedullary lesions which were treated with a PD-1 inhibitor.

Biopsy Fixation Details

Buffered Zinc Formalin/Formical

Frozen Tissue Available

No

Details of Microscopic Findings

One month after the CAR T-cell infusion, a BM biopsy and flow cytometry, including minimal residual disease (MRD) flow, were negative for B-ALL but did show a minute focus (<1%) of atypical spindled cells within the periosteum, associated with hemosiderin. The marrow was otherwise normocellular (~70%) with trilineage hematopoiesis and no increase in blasts. A subsequent bone marrow biopsy showed increasing involvement (20%) by an atypical infiltrate of variably sized hyperchromatic cells with irregular nuclear membranes, prominent nucleoli, and ample eosinophilic cytoplasm.

Immunophenotype

Immunohistochemical stains revealed that the focus in the first biopsy was positive for CD68 and vimentin, with admixed CD8-positive T-cells. The infiltrate in the subsequent biopsy was positive for CD43, CD45(dim) and CD68, with a subset of cells expressing CD4 and CD163, while negative for CD1a, CD3, CD15, CD21, CD23, CD30, CD34, CD42B, CD56, CD117, CD123, CD19, CD79a, PAX5, TdT, MPO, cytokeratin AE1/AE3, S100, ALK, GATA1, IBA1, and desmin.

Cytogenetics

Not available

Molecular Studies

Adaptive Biotechnologies Clonoseq NGS MRD detected the same IgH, IgK, and IgL sequences in the subsequent biopsy as was seen in the prior B-ALL. A FoundationOne NGS mutation panel also revealed:

1) *NRAS* c.34G>A, p. G12S

2) *FLCN* c. 1177-1G>A, splice site 1177-1G>A

3) *POT1* c. 959C>G, S320

Proposed Diagnosis

Initial biopsy: B-lymphoblastic leukemia (B-ALL) with atypical histiocytic infiltrate after immunotherapy

Subsequent biopsy: Transdifferentiation of B-lymphoblastic leukemia (B-ALL) to histiocytic sarcoma

Interesting Feature(s)

Treatment with anti-CD19 CAR T-cells can result in tumoral therapy escape via antigen loss or transdifferentiation.Transdifferentiation has previously been reported in mature B-cell lymphomas following CAR-T therapy and in rare cases of B-ALL treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. This patient received multiple lines of treatment, however the immunomodulatory therapy may have played a role in precipitating this switch due to the close temporal relationship between the two events. The *NRAS* mutation may have also played a role as *MAPK* and *RAS* pathway mutations are frequently seen in histiocytic neoplasms. The *FLCN* and *POT1* mutations, which were not seen in the original B-ALL and are more common in nonhematopoietic tumors, may have had an impact as well.

EA4HP24-LYWS-90

“Pseudo-Richter Transformation” following cessation of BTK-inhibitor therapy”.

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Case Description

Case 1: An 84-year-old male with a history of bladder cancer and chronic lymphocytic leukemia (CLL) was on observation for approximately 4 years until he developed progressive thrombocytopenia, splenomegaly, and a left lower lobe lung nodule in February 2019. Fine needle aspiration of the lung nodule showed involvement by CLL/SLL, and the patient was started on ibrutinib. After 16 months on therapy, Ibrutinib was held a week prior to scheduled surgery in October 2020, when the patient underwent a left lower lobe superior segmentectomy combined with mediastinal lymph node dissection for newly diagnosed adenocarcinoma in the left lower lobe lung. Several of the excised mediastinal lymph nodes showed involvement by a diffuse large B-cell lymphoma. After the surgery, patient declined CLL or DLBCL directed therapy due to surgical complications and deconditioning. Strikingly, no FDG-avid disease consistent with DLBCL was identified in the mediastinum or any other site on 3 months and 12 month follow up imaging.

Case 2: A 58-year-old-man with history of thyroid cancer, renal cell carcinoma and pancreatic cysts was diagnosed with CLL/SLL in 2014 based on the biopsy of an enlarged porta hepatis lymph node. He remained on observation for low burden disease for 8 years until development of progressive, symptomatic splenomegaly warranting therapy. He started zanubrutinib in June 2022 and achieved an excellent response. After 15 months on therapy, he required zanubrutinib be withheld five days prior to scheduled prostatectomy for the newly diagnosed prostate adenocarcinoma. Unexpectedly, DLBCL was also noted on right pelvic lymph nodes excised as part of the staging. Patient tolerated treatment cessation without clinical signs of disease flare. He resumed zanubrutinib three days after the surgery and remained without any clinical symptoms. Due to high suspicion for “Pseudo-Richter Transformation”, he was not offered DLBCL therapy. Follow up PET/CT after one month showed no FDG avid disease and the patient continued to remain without any clinical evidence of active disease.

Biopsy Fixation Details

Formalin fixed paraffin embedded

Frozen Tissue Available

No

Details of Microscopic Findings

In both cases, lymph nodes showed effacement of normal architecture by a diffuse infiltrate of atypical lymphoid cells, intermediate to large in size with numerous mitoses.

Immunophenotype
In both cases, lymphoma cells are positive for CD20, PAX5, BCL2 and negative for CD10, BCL6, cyclinD1, MYC. Additionally, lymphoma cells are positive for MUM1 and CD5 in case 2, while they are negative for MUM1 with only a subset showing CD5 expression. Ki67 Proliferation index is 50% and 90%, respectively, in case 1 and case 2.
Cytogenetics
In both cases, FISH studies are negative for rearrangements in BCL6, MYC, BCL2 genes. Cytogenomic microarray analysis (CMA) detected trisomy 12 in a mosaic state (30% of cells) in case 1, while showed gain of chromosome segment 1q21.3 (100% of the cells) in case 2.
Molecular Studies
NGS studies detected Tier 2 mutations in BCOR and TET2 genes, respectively, in case 1 and 2.
Proposed Diagnosis
Pseudo-Richter transformation of CLL/SLL following BTK-inhibitor withdrawal
Interesting Feature(s)
Both patients received BTK inhibitor for nearly 15-16 months prior to withdrawal, and demonstrated an incidental finding of lymph nodes with histologic evidence of DLBCL following its cessation. Despite these histologic findings, neither patient had clinical signs or symptoms of transformation. Furthermore, cytogenetic, molecular studies and follow-up PET/CT scans did not demonstrate any evidence of progression.

EA4HP24-LYWS-93

CAR-T Complications

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Case Description
A 31 y o old male presented with adenopathy in 2016. The right cervical lymph node biopsy showed Follicular lymphoma, grade 1-2 of 3. Clinically stage II. He was treated with XRT 30gy. In 2018, he presented with a mass in the left axilla compatible with recurrence. He was treated with Bendamustine and Rituximab. In Nov 2021, he presented with a lesion in his left foot (Talus) bone. Biopsy was c/w Large B cell Lymphoma. He was treated with R-CHOP (x6). In July 2022, a follow up PET scan of the Talus bone demonstrated a Daeuville 5 lesion– suspicious for residual active lymphoma and he was further treated with HD MPx3 days and Rituxan, and RT 30gy in 10 fractions. Follow up PET CT showed resolution of the Talus lesion. However, multiple additional osseous lesions were seen. He was considered a candidate for Chimeric Antigen Receptor (CAR)-T and in Oct 2022, started treatment with CAR T Yescarta infusion. In April 2023, he presented with a large left lower extremity 20 cm mass. PET CT showed intensely increased FDG activity extending from proximal tibial shaft to distal one third of the tibial shaft, consistent with active lymphoma. A biopsy showed an

atypical T CD3+, CD8+ T cell proliferation infiltrating skeletal muscle. There was no evidence for B cell lymphoma. Between Apr-May when he presented with this mass and follow-up appointment in July, the mass resolved spontaneously without treatment.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

NA

Details of Microscopic Findings

2016: Lymph node biopsy contained back-to-back nodules with mostly centrocytes c/w with Follicular lymphoma, Grade 1-2 of 3.

2018: Left axilla node core biopsy morphology and flow analysis c/w relapsed Follicular Lymphoma, Grade 1-2 of 3.

2021: Left Talus bone core biopsy showed large transformed CD20+ B lymphocytes with vesicular nuclear chromatin, prominent nucleoli. There was necrosis. Ki-67 at 60 to 80% c/w Large B cell Lymphoma

2023: Left lower extremity mass (small core biopsies) showed a diffuse proliferation of small mature T lymphocytes. Diagnosis: Atypical T cell proliferation of unclear significance. Negative for B cell lymphoma.

Immunophenotype

Follicular lymphoma: CD20+, CD10+, BCL6+, BCL2+

DLBCL: CD20+, high KI67

Atypical T cell proliferation: CD3+, CD8+, CD2+, CD5+, high Ki-67 (80%)

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Atypical T cell proliferation representing a delayed CAR-T cell response.

Interesting Feature(s)

We report for the first time a self-resolving huge 20 cm mass; iatrogenic- therapy induced lesion. As of Jan 2024, patient is doing well with no disease.

This may represent an extramedullary presentation of T cells as seen in the bone marrows of post CAR-T treated patients; McFerran, J; Lytle, A; Gebre, K; Blood 2021.

i) Increased CD3+CD8+ T cell infiltrates in the bone marrow post CAR-T compared to pre CAR-T treatment bone marrow,

ii) Increased T cell infiltrates were seen in sustained responders to CD19-CAR compared to individuals with CD19-positive relapses and non-responders.

November 28, 2023: FDA investigates "Serious Risk of T-cell Malignancy Following CD19-Directed Autologous (CAR) T cell Immunotherapies", and is evaluating the need for regulatory action. 20 cases have been reported since the approval of CAR-T therapy in 2017, including 15 from the FDA's self-reporting adverse event system. Less familiarity with these lesions may have resulted in similar cases reported as T cell lymphomas following CAR-T.

EA4HP24-LYWS-97

Early histological large cell change (pseudo-Richter transformation) in patient with B-CLL/SLL with ibrutinib treatment interruption for unrelated surgery – incidental finding and diagnostic pitfall

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Case Description

Seventy-four-year-old male with known diagnosis of B-CLL/SLL underwent surgery for recurrent cutaneous squamous cell carcinoma of the left cheek including cervical lymph node resection. There were overall six lymph nodes detected measuring 8 - 12 mm.

All lymph nodes were infiltrated with predominantly large B-cell lymphoproliferation with non-GC phenotype and initially the diagnosis of Richter transformation was rendered. However, clinically the patient did not show any other features of progression and additional information of ibrutinib treatment and its interruption was revealed. Thus, the possibility of early histological features of pseudo-Richter large cell change related to ibrutinib treatment and its interruption was suggested.

Biopsy Fixation Details

EDTA for bone marrow, buffered formalin for lymph node.

Frozen Tissue Available

No.

Details of Microscopic Findings

Lymph node (B24498/22): Lymph node showed effaced architecture, mostly with diffuse proliferation of larger cells including prolymphocytes, centroblasts and immunoblasts. Few residual smaller cells were admixed in the background. Focal residues of nodular architecture resembling enlarged proliferation centers were seen. Increase in mitotic as well as apoptotic activity was observed.

Trephine biopsy (B4783/20): Bone marrow with almost diffuse intersticial infiltration by B-CLL/SLL is seen, slides provided for diagnostic assurance and potential further testing.

Immunophenotype

Phenotype of large B-cells – CD20++ CD19+++ CD23+++ CD5+ MUM1++ bcl2+++ cMYC (++/20%) Ki67 60-70%

Cytogenetics

Data from clinical report (2016) for B-CLL/SLL – two populations of cells:

1) del 11q (60% nuclei)

2) duplicated chromosome 8, del 11q (88% nuclei), del 13q (38% nuclei)

Molecular Studies

Data from 2020 for B-CLL/SLL – IgVH umutated, TP53 wild-type

Proposed Diagnosis

Early histological large cell (pseudo-Richter) change in B-CLL/SLL following ibrutinib treatment and/or interruption.

Interesting Feature(s)

Treatment by ibrutinib can cause changes in B-CLL/SLL such as increased number of large cells, diffusely expanded proliferation centers, and high mitotic rate and Ki67 proliferation index. Pseudo-Richter transformation is recently described phenomenon following temporary cessation of ibrutinib treatment combining clinical and histological features of RT. Presented case shows accidentally detected isolated histological large cell changes that were suggestive of Richter transformation and without the previous knowledge of ibrutinib therapy posed a potential diagnostic pitfall.

EA4HP24-LYWS-107

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Lymphadenopathy

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Case Description

A 35-year-old woman developed cough for which she received several antibiotics, including azithromycin, after which she developed pruritic rash, lymphadenopathy, and high fever. The patient underwent a skin biopsy which revealed a non-specific urticarial pattern; she then underwent cervical lymph node excisional biopsy.

Biopsy Fixation Details

The excisional specimen was fixed in 10% buffered formalin and slides of 4-6 µm sections were cut from formalin-fixed paraffin embedded tissues.

Sections were stained with hematoxylin and eosin and immunohistochemistry was performed using standard procedures.

Frozen Tissue Available

Not applicable

Details of Microscopic Findings

Enlarged encapsulated lymph node with a distorted and vaguely nodular architecture, increased vascular proliferation, eosinophilia, and a mild amount of sclerosis.

Immunophenotype

Flow cytometry analysis results: The lymphocyte gate contained 98% of total events of which 31% were CD19/CD20 positive B-cells with a kappa/lambda ratio of 1.7, 64% were CD3-

positive T-cells with a CD4/CD8 ratio of 4.2. No monotypic B-cell or aberrant T-cell population was identified.
Stains: EBER & CMV stains were negative.

Cytogenetics

Negative for genetic aberrations by conventional karyotype analysis and FISH panel for eosinophilia.

Molecular Studies

Negative for genetic aberrations using next generation sequencing analysis (lymphoid & myeloid panels).

Proposed Diagnosis

DRESS lymphadenopathy

Interesting Feature(s)

DRESS lymphadenopathy mimicking T-cell lymphoma features, particularly angioimmunoblastic T-cell lymphoma

EA4HP24-LYWS-124

Two distinct lymphomas in a patient with long-standing iatrogenic immune suppression for Crohn's disease

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Case Description

A 70 yo man with a history of Crohn's disease presented with fever, weight loss and fatigue. His history included treatment with adalimumab +azathioprine (2013-2016), certolizumab +azathioprine (2016-2018), infliximab +azathioprine (2018-2021). PET scan revealed nodules and masses throughout both lungs, bone marrow, spleen, liver, pancreas, lymph nodes, bilateral kidneys, soft tissue foci, and brain. He also met criteria for diagnosis of hemophagocytic lymphohistiocytosis (HLH) with fever, hyperferritinemia, hypertriglyceridemia, and markedly elevated soluble IL-2 receptor. Lung biopsy and bone marrow biopsies were performed.
He was treated with R-CHOP x 6 cycles as well as intrathecal methotrexate. PET CT showed resolution of disease.
2 years later, no longer on any immunosuppressive therapy, he presented with weight loss and was found to have and a LN biopsy was performed.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Lung 2021: Diffuse infiltrate of intermediate to large monotonous cells with vesicular chromatin and abundant pale cytoplasm. Necrosis. Focal angiocentricity.

BM 2021: Hypercellular with hemophagocytosis. No lymphoma.

LN 2023: Diffusely effaced by intermediate and occasionally large pleomorphic cells with hyperchromatic nuclei.

Immunophenotype

Lung 2021: CD79a+/EBER+ B cells with dim/partial CD20. Negative for CD138 and no staining with kappa or lambda to suggest plasmacytic differentiation. CD10-/BCL6+/MUM1+. CD30 negative. Very few background T cells.

LN 2023: CD3+/TCRBF1+ T cells that express CD2, CD4, CD5, CD7(dim) and CD279. Very few B cells. EBER negative.

Cytogenetics

FISH on DLBCL negative for *MYC*, *MYC*::*IGH*, *BCL2*, and *BCL6* rearrangements.

Molecular Studies

T cell lymphoma, 2023: Clonal T cell gene rearrangement in polyclonal background

Proposed Diagnosis

1. Iatrogenic immunosuppression associated B cell LPD, best classified as EBV+ DLBCL.
2. Peripheral T cell lymphoma, NOS, in a patient with an extensive history of iatrogenic immune suppression.

Interesting Feature(s)

The EBV+ B cell LPD was challenging to classify although clearly presented with extensive and aggressive disease. Polymorphic EBV+ B cell LPD as well as EBV+ MALT lymphoma were both considered. Ultimately we called this DLBCL given the lack of truly polymorphous B cell background. The extensive disease and HLH necessitated rapid treatment as an aggressive lymphoma beyond what reduction in immune suppression alone would accomplish. His PTCL, 2 years later, while off immune suppression, raises interesting questions about the long-standing effects of these medications on the immune system and whether to classify this as an iatrogenic immunodeficiency associated lesion.

EA4HP24-LYWS-138

Pattern approach of lympadenomegalia of HIV-positive patient

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Case Description

A 35-year-old HIV-positive male treated with antiretroviral therapy came to University Clinical Center of Vojvodina with symptoms of night sweating, fever and weight loss.

Cervical lymph nodes enlargement had been noticed for 6 months. Additional imaging showed mediastinal tumor mass. Firstly, cervical lymph node biopsy was performed and report was consistent with EBV-positive lymphoproliferative disorder (LPD). Performed clonality of T- and B-cell population proved EBV related-LPD. Considering CHL as a differential, the clinicopathological correlation was warranted or another biopsy. Patient became anaemic with progression of symptoms and lymphadenomegaly, spleen enlargement and focal infiltration, without bone marrow infiltration. Rebiopsy of another cervical lymph node was indicated and corticosteroid therapy which resulted in patient's clinical improvement.

The second biopsy reported EBV-positive DLBCL, NOS. The patient was treated with R-CHOP and after the 3rd cycle partial response was achieved. After the 5th course he came down with abdominal pain and fever, focal liver infiltration, abdominal and mediastinal lymphadenopathy consistent with progressive disease. Salvage R-DHAP therapy was given, but in a period of posttherapeutic aplasia, the patient tested SARS-CoV2 positive and chest radiography registered massive pneumonia. The patient was treated with antimicrobial and supportive therapy. Control scans revealed resolution of hepatic lesions and abdominal lymphadenopathy, but he passed away one month later due to respiratory deterioration and multiorgan failure.

Biopsy Fixation Details

The tissue was fixed in 10%-buffered formalin for 24 hours.

Frozen Tissue Available

Unavailable.

Details of Microscopic Findings

Cervical lymph node biopsy showed morphology and immunophenotype of EBV-positive LPD. It was described as diffuse growth pattern of predominantly medium atypical lymphoid cells with many large cells of immunoblast morphology type. Also, some cells of classical HRS cells morphology were present. In background were lymphocytes, histiocytes, eosinophils and plasma cells with no necrosis. Bone marrow showed reactive changes. Having performed appropriate morphological and immunohistochemical analyses, the second cervical node biopsy report was EBV-positive DLBCL, NOS. The atypical lymphoid cells were of medium and large size with single sparse HRS-like cells.

Immunophenotype

First biopsy showed medium atypical lymphoid cells with many large cells of immunoblast morphology among some expressed B—cell markers such as CD20, PAX5, CD79a and EBER positivity and other expressed T-cell markers like CD2, CD3, CD5, CD7, CD4, CD8, CD43 and GranzymeB. Ratio of medium atypical lymphoid B-cells and T-cell was 1:1. Classical HRS cells morphology showed partly CD30 expression and CD15 negativity. In addition, clonality of T- and B-cell population was done and the report stated EBV related-LPD, but that could also be CHL as a differential, so the clinicopathological correlation was warranted or another biopsy. The second biopsy concluded EBV-positive DLBCL, NOS with medium and large atypical lymphoid cells and single HRS-like cells expressing CD20, PAX5, MUM1, EBV and CD30-focally positivity with proliferation index Ki67 about 30-40%.

Cytogenetics

Unavailable.

Molecular Studies

Unavailable.

Proposed Diagnosis

Mediastinal grey zone lymphoma.

Interesting Feature(s)

Diagnosis and classification of grey zone lymphoma remains challenging for both pathologist and hematologist. It is a rare hematologic malignancy that needs extensive sampling for correct diagnosis and is still subject to inter-observer variability.

EA4HP24-LYWS-149

Eosinophil-enriched lymphadenitis, most consistent with DRESS, in a post COVID-19 vaccination

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Case Description

79-year-old male with past medical history of prostate cancer, papillary thyroid carcinoma, and pseudogout (on allopurinol), presented with altered mental status, fever, rash, fatigue, cervical lymphadenopathy, anemia, and thrombocytopenia. He received a COVID-19 vaccine 7 days prior to admission. A skin biopsy from the rash was performed which showed findings consistent with drug rash with eosinophilia and systemic symptoms (DRESS), possibly associated with COVID-19 vaccine and/or allopurinol. Pertinent laboratory results at admission included Hgb 13.6 g/dL (L), platelets 74 x 10e3/uL (L), WBC 6.43 x 10e3/uL (N), albumin 2.8 g/dL (L), AST 61 U/L (H), ALT 67 U/L (H), ferritin 985.2 ng/mL (H), CRP 18.2 mg/dL (H), LDH 344 U/L (H), and negative fungal, bacterial and mycobacterial cultures. An excisional lymph node biopsy was performed after a lymph node core biopsy showed only non-significant findings.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections showed fibrofatty tissue with areas of coagulative necrosis and a dense mixture of inflammatory cells including a significant number of plasma cells, eosinophils and small lymphocytes. Scattered larger cells, multinucleated cells, and apoptotic debris were also present. Associated small lymph nodes were identified, which showed relative

retention of the architecture including the presence of patent sinuses and paracortical hyperplasia.

Immunophenotype

Immunohistochemical staining demonstrated a mixture of CD20+, PAX5+ B cells and CD3+ T cells, with scattered histiocytes and macrophages, the latter of which were variably detected by CD68 and S100. In addition, the plasma cells were polytypic. In situ hybridization for the Epstein Barr virus (EBV; EBER probe) showed the presence of a significant number of positive cells.

Cytogenetics

N/A

Molecular Studies

Paraffin tissue was used for IGK, IGH and TCRg PCR analysis. For the IGH and TCRg assays, several distinct peaks were identified in two independent reactions which were randomly distributed with different migration rates, consistent with the presence of a few B or T cells, respectively, (pseudoclonal pattern). For the IGK assay, clonal peaks in a polyclonal background were identified in duplicate reactions, results compatible with a B-cell lymphoproliferative disorder or clonal excess in a reactive B-cell proliferation (latter favored).

Proposed Diagnosis

Eosinophil enriched necrotizing reactive lymphomatoid lymphadenitis with evidence of Epstein Barr virus reactivation most consistent with drug reaction with eosinophilia and systemic symptoms (DRESS).

Interesting Feature(s)

We are presenting a case of a patient on long-term allopurinol who developed signs and symptoms and tissue biopsy findings most consistent with DRESS, who significantly had a COVID-19 vaccination shortly before the development of his symptoms.

While the temporal association between DRESS and COVID-19 vaccine is not fully understood, cases describing COVID-19 mRNA vaccine-associated DRESS have been reported (PMIDs: 36424905, 35550918, 36514624). It is important to note that the patient had also been receiving allopurinol, a drug known as a common cause of DRESS.

Additionally, a significant number of EBV-positive cells were present, suggesting viral activation/re-activation, most likely secondary to DRESS -associated immune dysregulation.

Clinically, the allopurinol was discontinued and the patient was started on IV methylprednisolone, followed by significant improvement of his mental status, strength, fevers and liver function test. The patient was discharged and is doing well.

EA4HP24-LYWS-173

An EBV+ polymorphic lymphoproliferative disorder arising in the setting of iatrogenic immunosuppression (chemotherapy/radiation therapy)

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Case Description

A 47-year-old female presented with dysphagia. Subsequent esophagogastroduodenoscopy showed a large ulcerating mass with bleeding in the lower third of the esophagus. Biopsy showed invasive moderate differentiated adenocarcinoma. CT scan showed abnormal asymmetric thickening along the distal aspect of the esophagus. PET scan revealed hypermetabolic distal esophageal wall thickening with an SUV of 32.3. Bilateral axillary lymph nodes were noted to have a low level activity with a maximum SUV of 0.7. She had an endoscopic ultrasound and was staged as IIIA. She received neoadjuvant chemotherapy (carboplatin and docetaxel) and received a total of 4680 cGy in radiation prior to an esophagogastrectomy and resection of lymph nodes. The surgery occurred approximately four months after the start of chemotherapy and one month after the end of chemotherapy and radiation treatment.

Biopsy Fixation Details

Representative sections of the resection specimen were fixed in formalin.

Frozen Tissue Available

Yes

Details of Microscopic Findings

Microscopic findings show multiple lymph nodes with focal areas of necrosis. These foci are associated with a polymorphous cell population including plasmacytoid / plasma cells, larger lymphocytes, and small lymphocytes. In areas away from the necrosis, the lymph node architecture is overall intact. In the wall of the esophagus, there is also a significant, predominately plasma cell, but also lymphoid, infiltrate. Although germinal centers are present, the plasmacytoid / plasma cells are seen infiltrating in the muscle. Focally groups of larger transformed cells with apoptotic debris are seen. There is no evidence of residual adenocarcinoma in the esophagus, stomach, or lymph nodes.

Immunophenotype

Immunostaining shows CD20+, PAX5+ B-lymphocytes primarily in follicles and near the necrosis with a predominant CD3+ T-lymphocyte population in the interfollicular areas. The follicles are CD10+, BCL6+, BCL2- with relatively intact follicular dendritic cell meshworks (CD21), most consistent with reactive follicles. Immunostaining for CD20 shows positivity in the areas of necrosis as well as some CD21 expression. No cytokeratin positive cells are seen in the areas of necrosis. Scattered CD123+ cells are identified away from the necrosis. EBER in situ hybridization and immunostaining for LMP1 highlight admixed EBV-positive cells,

which are increased closer to the necrosis. Plasma cells are polytypic by kappa and lambda immunohistochemistry. P53 highlights scattered cells only.

Cytogenetics

No cytogenetics studies were performed.

Molecular Studies

DNA studies were performed on two blocks which each contained lymph node tissue with EBV+ cells associated with necrosis. These samples showed the presence of the same clonal B cell population in a background oligoclonal B cell population by Ig heavy chain studies in both blocks.

Proposed Diagnosis

Based on morphology, immunophenotypic analysis and molecular genetic studies, this case is best classified as a polymorphic lymphoproliferative disorder, EBV+, arising in the setting of iatrogenic immunosuppression (chemotherapy/radiation therapy).

Interesting Feature(s)

This case demonstrates a polymorphic lymphoproliferative disorder that developed after treatment of a primary solid malignancy with chemotherapy. Lymphoid proliferations and lymphomas arising in post chemotherapy regimens for previous solid or hematological malignancies are increasingly being recognized as a significant immune deficiency and dysregulation setting. This case highlights the importance of maintaining a high suspicion for these lesions in resection specimens of these patients.

EA4HP24-LYWS-186

Therapeutically Tenacious T cells: Accelerating CARs Parking in the CNS and GI

Dr. Jaryse Harris[1], Dr. Adam Bagg[1], Dr. Danielle Fortuna[1], Dr. Joseph Fraietta[2,1], Sonia Ndeupen[4], Dr. Marco Ruella[3,2], Dr. Adam Cohen[3]

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Case Description

74-year-old man with relapsed/refractory multiple myeloma status post multiple lines of therapy ultimately treated with anti-BCMA CAR T cell therapy. Two weeks post-infusion, the patient developed marked hyperleukocytosis with absolute lymphocytosis of CD3+ CD4+ T cells with variable loss of CD7 and CD5. Two months post-infusion altered mental status led to a lumbar puncture that showed a similar lymphocytic infiltrate. Ongoing diarrhea (3.5 months post-infusion) prompted GI biopsies showing absent plasma cells and

chronic epithelial injury mimicking CVID. Restaging bone marrow biopsy showed no plasma cells and increased lymphocytes (56%), predominantly T cells (99%).

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

NA

Details of Microscopic Findings

PB: Small mature appearing lymphocytes including variant lymphocytes.

CSF: Abundant small mature lymphocytes with occasional larger activated forms.

GI: Duodenum with epithelial injury (abundant crypt epithelial apoptosis and mucin depletion) in a background of chronic mucosal injury (villous blunting, atrophy, foveolar metaplasia). Terminal ileum and colon also with epithelial injury (crypt epithelial apoptosis) and features of chronic mucosal injury (crypt architectural distortion, ileal villous atrophy).

BM: Aspirate shows increased small mature-appearing lymphocytes (56%), some with eccentric nuclei. Biopsy is limited, non-contributory.

Immunophenotype

PB: Flow cytometry - 86% lymphocytes, including 45% CD3+ CD7-(variable to absent) CD2+ CD5+ (minor subset loss) CD4+ CD8- anti-BCMA CAR+ T-cells.

CNS: Flow cytometry - 99% lymphocytes, 84% CD3+ CD4+ T cells with no overt abnormalities, other than variable diminution in CD7.

GI: IHC - CD138 shows absent plasma cells; RNA-scope - anti-BCMA CAR+ T-cells.

BM: Flow cytometry - 99% of lymphocytes are T cells, mostly unremarkable (CD4:CD8 ratio: 5.5, minor subset, 7.5%, CD7- CD4+ cells).

Cytogenetics

BM: Normal karyotype.

Molecular Studies

TRG analysis by PCR and NGS on PB, CSF and BM: no evidence of clonality

NGS: Variants of Uncertain Significance:

- CREBBP p.V238L; c.712G>C; NM_004380.2 (VAF: 51%)
- MPL p.V368L; c.1102G>T; NM_005373.2 (VAF: 49%)
- PALB2 p.A968G; c.2903C>G; NM_024675.3 (VAF: 49%)

Proposed Diagnosis

PB: Exuberant reactive expansion of therapeutic T cells

CSF: Marked infiltration of therapeutic T cells

GI: Mucosa with immune-mediated injury pattern and markedly reduced to absent plasma cells

Interesting Feature(s)

- Striking PB T cell lymphocytosis, mimicking a T cell neoplasm (which has been described in other patients following CAR T therapy) reflecting an unusually sustained polyclonal therapeutic CAR T cells expansion.
- Neurologic symptoms due to extensive CSF involvement by similar cells.
- GI biopsies show immune-mediated injury, resembling CVID.
- Probable germline SNPs may have contributed to the sustained CAR T cell expansion.

- As cellular therapy utilization increases, judicious interpretation of flow cytometric, morphologic and histologic findings becomes paramount, to evaluate for (and exclude) T-cell neoplasms, as well as to recognize novel mimicking pathologies.

EA4HP24-LYWS-188

Cervical lymphadenopathy in a patient on dasatinib and bosutinib

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Case Description

45-year-old man with chronic myelogenous leukemia (CML) who was treated and had a complete cytogenetic response in 2012. In June 2013, while on dasatinib, he developed cervical lymphadenopathy. Core biopsies showed follicular hyerplasia. Dasatinib was discontinued 1/2014 and the lymphadenopathy resolved within one month. He was started on bosutinib and new right neck lymphadenopathy developed. An excisional biopsy was performed.

Biopsy Fixation Details

AZF and formalin fixation. The formalin fixed slides were submitted.

Frozen Tissue Available

n/a

Details of Microscopic Findings

Sections demontrated back-to-back large follicles, some serpiginous and irregular and PTGC-like, containig attenuated mantle zones, tingible body macrophages, and a mixture of centrocytes and centroblasts.

Immunophenotype

The atypical follicles are positive for CD20, CD10, and BCL6. BCL2 is negative.
Flow cytometry showed lambda-restricted, CD10 positive B-cells in a polyclonal background.

Cytogenetics

Normal karyotype.
Array CGH showed loss of 3.47 Mb at 1p36.32p36.31. This loss involes 31 genes including *TNFRSF14, PRD16 and TP73*.
The deletion was confirmed by FISH in 48% of cells.

Molecular Studies

n/a

Proposed Diagnosis

Atypical follicular hyperplasia, dasatinib and bosutinib-related.

Interesting Feature(s)

Similar lymphoid proliferations have been reported in the context of dasatinib therapy (Ozawa et al 2015; Roux C et al. 2013) including one case with a cytogenetic abnormality. Our case resembles the morphologic features presented by Ozawa and colleagues. It is hypothesized that both medications could lead to lymphadenopathy since these TKIs have the strongest SFK inhibition and this has been shown to lead to lymphocyte proliferation (Turhan et al 2013). However, the morphology, flow findings, and the array CGH/FISH results could also support the diagnosis of pediatric follicular lymphoma in a patient without a history of TKI therapy. No lymphadenopathy occurred after excisional biopsy and cessation of both dasatinib and bosutinib.

EA4HP24-LYWS-203

DRESS Syndrome

Prof. Arzu Saglam Ayhan, Prof. Aysegul Uner

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Case Description

19-year old female, admitted with skin rash, continuing nausea and vomiting (Sept 2022)

- History of medical evaluation for nausea and vomiting, was diagnosed with urinary tract infection and prescribed cephalosporin. She developed disseminated skin rash and pruritis two days into treatment. Treatment was ceased and patient was given pheniramin and methyprednisolone whereupon her symptoms partially resided. She stopped this medication a day before seeking care in our hospital
- Past medical history significant for epilepsy (diagnosed May 2022), eventually controlled with the following medications
  - Levetirecetam
  - Carbamazepine (initiated a 1,5 months ago; nausea and vomiting started 1,5 weeks after initiation of carbamazepine)

Initial work-up at our hospital

- Found to have fever and hypotension
- Lab
  - LFTs abnormal (increased ALP, GGT, AST, ALT, indirect bilirubin, bilirubin)
  - Leukocytosis (16100 /µl) with eosinophilia
  - Hemoglobin normal
  - Platelet counts normal
  - CRP, d-dimer increased, C3 & C4 low
  - Cultures (blood, urine, sputum, pleural fluid) - negative
- Imaging

- Pleural effusion, pulmonary edema, peritoneal fluid, disseminated lymphadenopathy reaching 40x16,5mm, no hepatosplenomegaly
- Increased FDG of lymph nodes, bone marrow and spleen

- Given phenyramine + methylprednisolone +pantoprazole in the ER

Diagnosed as DRESS syndrome

- Methylprednisolone 40mg/day iv
- Lymph node biopsy while on methylprednisolone
- **Follow-up**
- Bone marrow – normocellular
- Anti-epileptic medication readjusted
- Discharged on deltacortril and prednisolone, followed by tapered discontinuation over 6 months
- Diagnosed with hypothyroidism and thyroid medication added
- Diagnosed with and treated for myocarditis a year after discharge (September 2023)

Biopsy Fixation Details

72 hours 10% formaldehyde

Frozen Tissue Available

No

Details of Microscopic Findings

Biopsy demonstrated effacement of lymph node architecture with lack of well-formed cortical follicles and unidentifiable germinal centers. Interfollicular area was markedly expanded by a polymorphic population composed of predominantly of histiocytes with accompanying sentroblastic and immunoblastic large lymphoid cells as well as small lymphocytes and plasma cells. Hemophagocytic activity was noted, most noticable within the subcapsular sinuses. Foci of necrosis, karyorrhexis and apoptotic debris could be identified. Chunks of karyorrhexis and apoptotic debris could also be seen plugging the pericapsular vasculature.

Immunophenotype

Immunohistochemical examination (BenchMark Ultra IHC/ISH system by Roche Ventana) highlighted expansion of interfollicular T-cell areas with CD3. The B cell areas were seen to be pressed to the periphery with the CD20 stain. Intact dendritic network corresponding to the B cell areas with CD21 and CD23. CD4 & CD8 showed predominance of CD4 staining, the larger lymphoid cells were CD8 positive as well as granzyme-B, CD30 and MUM-1. CD138 positive plasma cells were seen to be polytypical with kappa & lambda. PD-1 stained the follicular T-helpers within the B cell areas and were few. There were also very few CD123 positive cells. CD68 demonstrated increased macrophages. ALK, HHV-8, CMV and EBER staining was negative. No microorganisms identified with GMS, PAS & ARB histochemistry.

Cytogenetics

not done

Molecular Studies

No T cell clonality

Proposed Diagnosis

Atypical lympoid proliferation associated with DRESS syndrome

Interesting Feature(s)

This case demonstrates what can best be described as a Kikuchi-like pattern of lymphoproliferation associated with Dress syndrome. Presence of hemophagocytosis and apoptotic karyorrhectic debris within the vasculature is also interesting

EA4HP24-LYWS-218

Pseudo-Richter Transformation in the Setting of Presurgical Zanubrutinib Therapy Interruption in a Patient with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Case Description

Patient is a 73-year-old male with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (CD38(-), zap70(-), unmutated (V1-69), trisomy 12, not complex karyotype) diagnosed three years ago. He initiated treatment with zanubrutinib for abdominal lymphadenopathy up to 22.6 cm and ALC of 124K/uL. After 12 months of treatment, he demonstrated an excellent response, with normalization of his CBC and largest lymph node on PET scan of 2.1 cm. A new 1.8 cm cecal mass with SUV 26.7 was found, which on biopsy confirmed to be adenocarcinoma. He underwent a laparoscopic right hemicolectomy which demonstrated the tumor confined to the muscularis propria (pT2N0M0) with negative margins. Twelve lymph nodes were examined which showed atypical lymphocytes. Of note, zanubrutinib had been held for seven days prior to surgery to enable hemostasis. CBC showed WBC: 9.4 K/mL[3.4-11.2], Hgb: 13.0g/dL[13.7-17.5], MCV: 93.3 fL[80-100], PLT: 154 K/mL[150-450]

Biopsy Fixation Details

10% Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic examination showed lymph node tissue with architectural effacement by atypical lymphocytes. Areas of predominantly small-to-intermediate cells were seen. However, between these areas, medium-to-large sized cells were also seen with confluent growth. The large cells showed oval to irregular nuclear contour, vesicular to dispersed chromatin, prominent central nucleoli, and small amounts of cytoplasm, with frequent mitoses.

Immunophenotype

Immunohistochemical stains showed expression of CD20 (weak), PAX5, CD5 (weak to negative), BCL6 (weak), MUM1, BCL2, MYC, CD21, and CD23 in the medium-to-large sized cells. These cells were negative for CD10. Ki-67 showed a proliferation rate of greater than 80%. Majority of the cells were positive for p53 with variable expression. EBV-encoded RNAs by in situ hybridization was also negative.

Cytogenetics

Not performed.

Molecular Studies

DNA extracted from formalin-fixed-paraffin-embedded tissue was used for targeted hybrid-capture based next generation sequencing assay. *TP53* p. H233Tfs*13, *RNF43* p. P660Sfs*87, and *PTPN11* p.E76K were reported. Characterization of patient's peripheral blood previously had shown *PTPN11* p.E76K. B-cell clonality studies showed clonal rearrangement on *IGH*, *IGK*, and *IGL* by a next generation sequencing assay.

Proposed Diagnosis

Pseudo-Richter Transformation of CLL/SLL

Interesting Feature(s)

The histomorphologic and immunophenotypic findings raised the possibility of a large cell transformation of the patient's CLL/SLL. Pseudo-Richter transformation (RT) has been previously reported in patients following interruption of Bruton's tyrosine kinase (BTK) inhibitor therapy. It is thought to result from rapid proliferation that ensues after the release of BTK inhibition. The lack of significant lymphadenopathy seen on pre-operative imaging and normal CBC are supportive of a pseudo-RT. However, the presence of a new *TP53* mutation is worrisome for this being a true transformation and may be indicative of clonal evolution. Pretreatment prognostic markers did not identify any predictors for the development of RT (*NOTCH1* mutation, subset 8 stereotypy, *TP53* mutation, deletion 17p), which may indicate the inability for pretreatment characteristics to absolutely predict outcomes. Clonality studies on the initial CLL sample are pending for comparison, however the identical *PTPN11* variant is supportive. The patient has been restarted on zanubrutinib therapy and follow-up imaging is pending. While the lymph node findings were concerning for disease progression, clinical and radiologic correlation was crucial.

EA4HP24-LYWS-221

Pseudo-Richter Transformation in An Otherwise Clinically Silent Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Patient Following Temporal Acalabrutinib Interruption

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Case Description

A 60-old woman underwent hysterectomy and bilateral salpingo-oophorectomy and sentinel lymph node dissection for suspected endometrial neoplasm on 9/18/2023. She has a history of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with unmutated *IGHV* and wild-type *TP53*, and has been treated with acalabrutinib since November 2021. She was off acalabrutinib for a period of 7 days during peri-operative period (9/15/2023-9/21/2023).

Her pre-operative staging CT showed no lymphadenopathy in the pelvis. The post-surgical PET/CT scan on 9/27/2023 revealed no lymphadenopathy and FDG activity. Her post-surgical complete blood cell count (CBC) showed mild leukocytosis (WBC, 11.49-14.03 $x10^9$/L) and absolute lymphocytosis (5.86-9.26 $x10^9$/L) between 9/19/2023 and 10/2/2023 with a peak level at approximately day 9 post-surgery. Blood smear review showed proportionally expanded circulating large neoplastic cells with prominent nucleoli, concerning for large cell transformation.

Biopsy Fixation Details

3 hours in 10% neutral buffered formalin.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

Histologic sections of pelvic sentinel lymph nodes show an effaced nodal architecture by numerous expanded and confluent proliferation centers consisting of sheets of immunoblasts intermixed with scattered smaller para-immunoblasts and prolymphocytes at variable proportions (Image 1). Mitotic activity is brisk (~10 per high-power field). The capsule is intact and uninvolved. Extranodal extension is not appreciated.

Immunophenotype

By immunohistochemistry, both large and smaller neoplastic cells are positive for CD5 (weak, subset), CD20, CD23, CD45, BCL2, MUM1 (variable, ~80-90%), LEF1, MYC (~40%), and PAX5 (weak in large cells, strong in smaller cells), and are negative for CD10, cyclin D1, SOX11, BCL6 and PD1 (< 5% positivity). The neoplastic cells are variably positive for P53, mostly in the form of weak nuclear positivity. The neoplastic cells show kappa light chain restriction

by kappa and lambda in situ hybridization. A Ki-67 proliferation index is approximately 70-80% (Image 2).

Cytogenetics

Interphase FISH performed on FFPE sections revealed one extra signal of *IGH* but no rearrangement of *MYC* or t(8;14).

Molecular Studies

N/A

Proposed Diagnosis

Lymph nodes, bilateral sentinel obturator and pre-sacral, excision:
Chronic lymphocytic leukemia/small lymphocytic lymphoma with increased immunoblasts and expanded proliferation centers, compatible with pseudo-Richter transformation in the context of temporal acalabrutinib interruption

Interesting Feature(s)

- Pseudo-Richter transformation (Pseudo-RT) has been first recognized in CLL/SLL patients during temporary interruption of ibrutinib in small case series.
- The current case illustrates another nice example of pseudo-RT in an otherwise well-controlled CLL/SLL patient following acalabrutinib interruption.
- Despite the lymph nodes and peripheral blood showed morphologic features resembling those of large cell transformation, there was no clinical and radiographic concordance in disease progression.
- She resumed acalabrutinib on 9/22/2023, and her CBC was back to normal within two months.
- Recognition of pseudo-RT in CLL/SLL patients in the era of Bruton's tyrosine kinase (BTK) inhibitor therapy is critical to avoid overdiagnosis and overtreatment.

EA4HP24-LYWS-234

Extranodal marginal zone lymphoma in the setting of methotrexate therapy

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Case Description

The patient is a 69 y/o female with history of eosinophilic granulomatosis with polyangiitis (eGPA) and severe asthma. For 10 years, she has been on low-dose methotrexate. On chest CT, a 2cm nodule in the posterior right lower lobe of the lung was seen. Interval growth of the nodule was noted and she underwent surgical resection. A wedge biopsy of the main nodule was sent for frozen section, which was diagnosed intraoperatively as negative for carcinoma and dense lymphoid infiltrate. A wedge resection with lymph node dissection

was performed and the tissue was sent for flow cytometry. The surgical pathology sections and flow cytometric analysis revealed an atypical B cell population concerning for B-cell lymphoma. EBV was positive by EBER in situ hybridization (ISH) in scattered cells. B-cell clonality studies confirmed a monoclonal B-cell population. A diagnosis of extranodal marginal zone lymphoma was rendered. A subsequent bone marrow biopsy was negative for involvement by lymphoma. The patient remains asymptomatic; post-surgical imaging revealed no adenopathy or involvement of other organs by lymphoma. She resumed methotrexate therapy and continues under surveillance.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Sections revealed an atypical lymphoid proliferation involving lung parenchyma with nodular and diffuse patterns. Involvement was both peribronchial and perivascular. Germinal centers were present. Lymphocytes were predominantly small and mature with a plasmacytoid appearance. Few scattered single atypical large lymphoid cells were seen. No sheets or aggregates of large cells were seen. Scattered plasma cells including Mott cells were noted. Scattered non-caseating multinucleated giant cells with cholesterol clefts were present; rare giant cells contained polarizable foreign bodies. Eosinophils were not prominent and no vasculitis was noted. AFB, PAS, and GMS special stains were negative for infectious organisms. Congo red stains were negative for amyloid. Immunohistochemical stains revealed B-cells in a predominantly nodular pattern with no aberrant antigen expression and a low proliferation index (Ki-67) of 5-10%. Kappa and lambda ISH demonstrated lambda predominance. EBV by EBER ISH revealed scattered positive cells, including few of the large lymphoid cells.

Immunophenotype

Flow cytometry revealed an atypical B-cell population with immunophenotype: CD19, CD20 positive; light chain negative to very dim lambda positive.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Extranodal marginal zone lymphoma

Interesting Feature(s)

This case exemplifies an iatrogenic immunodeficiency-associated lymphoproliferative disorder by WHO-HAEM4R criteria or lymphoma in the immune deficiency/dysregulation setting by WHO-HAEM5 criteria. An atypical lymphoid proliferation consistent with low-grade B cell lymphoma was present; oncogenic viral positivity (EBV) was demonstrated by ISH; and the patient has a history of iatrogenic immunosuppression (methotrexate therapy). Molecular studies further confirmed a monoclonal B-cell population. The diagnosis of extranodal marginal zone lymphoma in the immune deficiency setting was rendered.

EA4HP24-LYWS-280

Extranodal diffuse large B-cell lymphoma in a child with a primary atopic disorder and a germline *PTPN13* variant receiving immunomodulatory therapy.

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Case Description

A 4-year-old female from Southeast Asia with a presumed inborn error of immunity (IEI) responsible for her primary atopic disorder (PAD) characterized by skin rash, diarrhea, and episodic acute respiratory distress syndrome, on ruxolitinib (JAK1/2 inhibitor) and dupilumab (IL4/13 inhibitor) therapy due to steroid refractoriness, came to our institution for evaluation for a stem cell transplant as she harbored a germline *PTPN13* variant. CBC revealed a WBC count of 6.63 x 10^3/uL, with 12% eosinophils, and hemoglobin of 9.9 g/dL. During the pre-transplant work up, an abdominal ultrasound (US) exam revealed a 6.4 cm solid mass involving the left lateral lobe of the liver with internal vascularity and calcifications. MRI showed a heterogeneous mass in segments 2 and 3 with peripheral enhancement. The patient underwent a US-guided liver biopsy that revealed a diffuse large B-cell lymphoma (DLBCL), clinically stage III. The patient was treated per ANHL1131 Group B protocol, but due to acute kidney injury, therapy was switched to DA-EPOCH, which is currently ongoing.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the liver mass biopsy showed a dense infiltrate of intermediate to large-sized pleomorphic lymphocytes with round, oval or irregular nuclei, fine chromatin, variably prominent nucleoli and scant cytoplasm. Admixed histiocytes and many small mature lymphocytes were present and scattered apoptotic cells and mitotic figures were observed.

Immunophenotype

Immunohistochemistry showed the following phenotype of the neoplastic lymphocytes: CD45+, CD20+, CD79a+, OCT2+, CD10(weak)+/-, BCL6+, HGAL+, LMO2(weak)+/-, MUM1+, FOXP1+/-, CD21-, CD43+/-, CD30-, CD15-, TdT-, CD123-, PD-L1-, PD-1-, and BCL2+/-. The Ki-67 labeling index was ≈50%. C-MYC+ and P53+ lymphocytes accounted for ≈10% and <5% of all cells, respectively. In-situ hybridization for EBER (EBV) was negative. A rich infiltrate of T-cells (CD3+, CD5+, CD43+) was observed in the background, with a prominent PD-1+ subset. Numerous PD-L1+ macrophages were also present.

Flow cytometry detected a population of lambda light chain restricted B-cells (≈12% of

total events/cells) with the following immunophenotype: CD20+, CD19+, CD79a+, CD22(weak)+/-, CD10(weak)+/-, CD23-, CD38+, CD9+, CD200-, CD58+, CD11c-, CD103-, CD43(weak)+/-, IgM-, and IgD-.

Cytogenetics

FISH was negative for *MYC*, *BCL2* and *BCL6* rearrangements or copy number abnormalities.

Molecular Studies

PCR analysis demonstrated a clonal IgH gene rearrangement.

Proposed Diagnosis

Diffuse large B-cell lymphoma, germinal center B-cell phenotype/cell of origin (by the Hans algorithm).

Interesting Feature(s)

Our case illustrates an extranodal DLBCL occurring in a child with a genetically uncharacterized IEI predisposing to a PAD being treated with JAK1/2 and IL4/13 inhibitors, who also carries a germline *PTPN13* variant. To the best of our knowledge, no DLBCLs have been described in pediatric patients treated with the aforementioned immune modulating drugs.

In adult patients with myeloproliferative neoplasms (MPNs), the frequency of B-cell lymphomas, including DLBCL, has been reported to be ≈5%, with the vast majority of DLBCLs arising in individuals receiving ruxolitinib. Hence, a contributory role of immune modulatory therapy in lymphomagenesis cannot be ruled out in our patient.

Germline pathogenic *PTPN13* variants are associated with bone marrow failure and lymphoblastic leukemia. Any cooperativity between the signaling pathways impacted by these variants and/or the PAD and immune modifiers that fosters the development of lymphoma remains to be determined.

EA4HP24-LYWS-286

Subcutaneous panniculitis-like T-cell lymphoma post immunotherapy

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Case Description

A 76-year-old female with an erythematous rash of the skin of the limbs, trunk, and face with swelling around the eyes and high-grade fever was admitted [Fig.1A]; these symptoms lasted for 2 weeks. No splenomegaly, cytopenias, lymphadenopathy, hypertriglyceridemia, or hypofibrinogenemia was observed. A skin biopsy was performed.From the previous

medical history, the patient remained under follow-up due to immunochemotherapy treatment for the progression of BRAF-mutated melanoma. In 2011, the primary skin melanoma of the right lower leg was removed [pT2aN(sn)0Mx, VLI0, PNI0, R0]. In May 2022, a recurrence was found in the right inguinal lymph nodes (lymph node 27 mm, melanoma metastasis with perinodal fat tissue infiltration), and three cycles of nivolumab treatment (480mg) were administrated. In September 2022, the progression of melanoma infiltration in the inguinal lymph nodes (nodal conglomerate 48mm SUV 18.89 in PET-CT) led to the decision to initiate combined treatment with nivolumab and ipilimumab. Due to cardiotoxicity (increase in troponins, transient reduction in LVEF to 35%, episode of transient ischemic stroke), steroid therapy was initiated; after improvement, nivolumab treatment (480mg) was continued until February 2023 (complete remission is maintained in follow-up imaging tests) and the patient remained in good overall condition till July 2023 when skin problem and general symptoms started.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

not-available

Details of Microscopic Findings

Skin biopsy shows a lobular panniculitis image in the subcutaneous tissue; the infiltration comprises atypical lymphocytes arranged concentrically around adipose tissue cells, numerous mitotic figures, apoptotic cells, and foci of fibrinous necrosis are visible [Fig.1B].

Immunophenotype

The immunoprofile of infiltration is: LCA/CD45(+), CD3(+), CD8(+)>>CD4(-/+), GranzymeB(+), TIA1(+), CD43(+), CD15(-) positive in neutrophils, CD30(-), EBER(-), CMV(-), PAX5(-) and CD20(-) positive in scattered B-cell lymphocytes, MUM1(-) positive in scattered polyclonal plasma cells, CD68(-)/CD163(-) positive in macrophages, SOX10(-), Ki67(+) in 80% of cells [Fig.1C].

Cytogenetics

not-available

Molecular Studies

not-available

Proposed Diagnosis

Subcutaneous panniculitis-like T-cell lymphoma [SPTCL]

Interesting Feature(s)

The differential diagnosis is challenging since it overlaps with the skin-related reactions to immune checkpoint inhibitors. Clinically both lesions may have the same presentation. Histopathologically, the hemophagocytic syndrome limited to the skin related with post immunotherapy reaction or secondary to SPTCL was also difficult to separate and was within the spectrum of the presented image.

EA4HP24-LYWS-291

Dasatinib-associated lymphadenopathy in a patient with chronic myeloid leukaemia

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Case Description

A 66-year-old patient with BCR-ABL1 positive chronic myeloid leukaemia (CML) was treated since 2022 using Imatinib GLIVEC, which was discontinued due to allergy (muscle cramps, leg phlebitis). In August 2023, he was then treated with Dasatinib SPRICEL. After two months of dasatinib, he presented with a right laterocervical lymph node cast, accompanied by hypermetabolic adenopathy in the right axilla and in the right external iliac. The most intense focus corresponded to the right axillary adenopathy: SUV max 20.72. The left axillary lymph node was excised and sent for histologic examination.

Biopsy Fixation Details

FFPE

Frozen Tissue Available

No

Details of Microscopic Findings

The specimen measured 20 x 12 x 7 mm. It displayed paracortical hyperplasia, predominating in interfollicular areas, associated with numerous immunoblasts, eosinophilic polynuclei, and hyperplasia of post-capillary venules. Follicles were of different sizes and maintained their normal polarity and tingible body macrophages in the germinal centers.

Immunophenotype

After immunohistochemical study, B- and T-cell populations were of normal distribution and in harmonious proportion. Germinal centers were highlighted by CD10 (low intensity) and Bcl-6 (high intensity). They were not stained by BCL2. Using CD23, the follicular dendritic cell framework was expansive. There was no aberrant cyclin D1 expression. Immunoblastic elements presented a CD20+ CD30+ phenotype. T-cells comprised over 80% CD4+ T-cells and 20% CD8+ -cells. There was no loss of CD7, CD2, or CD5 expression. There was no significant expression of PD1, ICOS or CXCL13. There was no plasma cell light chain restriction. Detection of EBV EBER latency RNA by in situ hybridization was negative. The proliferation index revealed by Ki-67 appears accentuated within the germinal centers.

Cytogenetics

No

Molecular Studies

Clonality analysis (BIOMED-2) showed no monoclonal B- or T-cell population.

Proposed Diagnosis

Dasatinib-associated lymphadenopathy (DAL).

In November 2023, dasatinib was stopped and switched for bosutinib. Lymph nodes and splenomegaly completely regressed spontaneously following cessation of treatment.

Interesting Feature(s)

The differential diagnosis in a CML patient with localized lymphadenopathy may present significant diagnostic challenges. Along with the typical workup, the exclusion of extramedullary blastic transformation of CML is warranted. Lymphoma has scarcely been described in the literature in CML patients, but patients on dasatinib treatment may present lymph node enlargement characterized by follicular hyperplasia, or, in some cases, paracortex expansion due to a heterogeneous population of eosinophils, plasma cells, histiocytes and immunoblasts, as described in our case.

In our patient, the highly hypermetabolic character of the adenopathies, as well as their chronology (appearance only after 2 months of treatment), were more suggestive of a lymphoma than of a reactive etiology. Indeed, according to published studies, dasatinib-associated adenopathies appear between 5 and 48 months after the introduction of the drug (14 months on average).

However, the histopathological findings, along with molecular data and the clinical course of the patient after drug cessation, prompted us to consider the possibility that drug-induced lymphadenopathy may be implicated in DAL.

The possibility of DAL should be considered if lymphadenopathy is observed during dasatinib treatment.

EA4HP24-LYWS-297

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: Cutaneous and lymph node findings

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Case Description

A 35 year old man with a history of end stage renal disease due to IgA nephropathy developed sepsis secondary to dialysis line infection and was treated with IV vancomycin during outpatient dialysis. One week after stopping antibiotics, he developed C. difficile colitis and oral vancomycin was initiated. Three days later, the patient again developed fever with altered mental status, tachycardia, hypotension, elevated liver function tests, and diffuse erythematous rash. MRI of the brain showed multiple watershed infarcts with petechial hemorrhage. CT studies showed adenopathy and splenomegaly interpreted as

suspicious for lymphoma. CBC data showed leukocytosis with relative and absolute eosinophilia. A skin biopsy and lymph node biopsy were performed.

Vancomycin was discontinued and solumedrol begun. Eosinophilia and fevers subsided. The patient was discharged and subsequently recovered without neurologic deficits.

Biopsy Fixation Details

Formalin fixation

Frozen Tissue Available

No

Details of Microscopic Findings

Skin: There is mild hyperkeratosis, acanthosis, and mild spongiosis. A perivascular and periadnexal infiltrate of small lymphocytes is present in the superficial and mid dermis, admixed with dermal eosinophils.

Lymph node: The nodal architecture is partially preserved with focally patent subcapsular and parenchymal sinuses. The paracortial areas are markedly expanded by an infiltrate of small lymphocytes, large transformed cells, occasional eosinophils and histiocytes. There is a prominent vascular proliferation throughout the paracortex.

Immunophenotype

Skin: Not performed.

Lymph node: Flow cytometric studies showed polytypic B-cells and heterogeneous T-cells (CD4:CD8 ratio =0.6). Immunohistochemical stains showed paracortical expansion by CD3 positive T-cells that were positive for CD2 and CD5 and showed slightly decreased CD7 expression. CD20 showed scattered aggregates of predominantly small lymphocytes. Approximately 30% of cells were positive for CD30. The T-cells included CD4 positive cells with similar numbers of CD8 positive cells. The majority of the T-cells showed variably intense staining for PD1 and a CXCL13 stain showed occasional positive small cells. CD21 highlighted irregular FDC meshworks. The T-cells were negative for TCL1a and ALK1. An EBV-LMP1 stain showed scattered positive small cells.

Cytogenetics

Skin: Not performed.

Lymph node: 46,XY[20].

Molecular Studies

Skin: Polyclonal TCRG and TCRB (BIOMED2 primers)

Lymph node: Polyclonal TCRG and TCRB (BIOMED2 primers)

Proposed Diagnosis

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

Interesting Feature(s)

DRESS syndrome is a severe, potentially fatal, drug reaction due to a delayed hypersensitivity response typically occurring within two to six weeks of initial drug exposure. Vancomycin has been reported to be a common inciting agent. Adenopathy raising concern for a lymphoproliferative disorder is frequent, and nodal histologic patterns are reported to include cases resembling angioimmunoblastic T-cell lymphoma (AITL), Hodgkin lymphoma, or Kikuchi's disease. This case exhibits histologic features that resemble AITL, but the T-cells do not exhibit a T-FH phenotype and a clonal T-cell

population was not identified by PCR. Knowledge of the clinical presentation and timing of the drug exposure is critical for correct diagnosis.

EA4HP24-LYWS-321

PTEN-related T-cell lymphoproliferative disease under chronic iatrogenic mTOR inhibition

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Case Description

The case concerns a 24-year-old man with Bannayan-Riley-Rubalcava syndrome. He was born with macrocephaly, cryptorchidism, multiple haemangiomas, 'café au lait' macules and visual defects.

A germline *PTEN* mutation (p.G36fs43X) was detected when he was 8 years old upon diagnosis of thyroid follicular disease, which evolved 3 years later to thyroid cancer (he was then treated with surgery and radioactive iodine). He has a normal germline karyotype.

The patient had been under sirolimus (3 mg per day) uninterruptedly for more than 10 years when he was admitted to our hospital.

He presented with painless cervical bilateral poliadenopathy (each more than 2 cm across), and afterwards axillary and inguinal too, with progressive enlargement. He had been having generalised pruritus for more than 6 months, but developed no skin lesions. No other signs or symptoms were reported (eg. lost weight, anorexia, fatigue, fever, sweating).

The PET-CT scan showed suspicious lymph-node uptake above and below the diaphragm, as well as heterogeneously in the spleen (although it was not enlarged).

From the laboratory work-up:

- LDH: 479 UI/L;
- Negative HTLV-1/2 IgG, HIV p24, CMV IgG/IgM;
- Serum EBV burden: 140 UI/mL;
- ANA titre: 1:160 (negative autoimmunity serology).

Biopsy Fixation Details

The lymph node excision specimen had a 24-hour fixation time in 10 % buffered formalin.

Frozen Tissue Available

No.

Details of Microscopic Findings

The lymph node's architecture is obliterated by a diffuse and monomorphous proliferation of small T cells, punctuated with small epithelioid non-necrotising granulomas, dispersed eosinophils and immunoblasts, and variably prominent endothelia. Also, there are large regressed (mantle-zone-only) lymphoid follicles with exhuberant dendritic networks.

Immunophenotype

By immunohistochemistry, the small T cells were CD3+, CD5+, CD2+, CD7+, CD4+, CD8–, CD10–, BCL6–, PD1+, ICOS–/+, and CXCL13–. EBER-ISH was negative.

By flow cytometry, the atypical T-cell population was detected both in the bone-marrow aspirate (2.7 %) and in a bronchoalveolar lavage sample collected during an infectious complication. The population was CD3+, CD5+/– (⅔), CD2+, CD7–, CD4+ (weak), and CD8–. A similar population, though CD5+, was found in peripheral blood (6.5 %).

Cytogenetics

No cytogenetic study was performed.

Molecular Studies

Three clonal *TRB* rearrangements and two clonal *TRG* rearrangements were found in fresh lymph-node aspirate. Only the *TRB* rearrangements were detected in the paraffin-embedded tissue.

The same two *TRG* rearrangements and two of the *TRB* rearrangements were detected in the bone-marrow aspirate.

No *IDH2, RHOA, TET2* or *DNMT3A* mutations—nor other common PTCL-associated mutations (in *CD28, IDH2, JAK1, JAK3, MSC, PLCG1, SETD2, STAT3, STAT5B, TNFRSF1B, TP53*, and *VAV1*)—were identified by NGS in the paraffin-embedded tissue.

Whole exome sequencing is forthcoming.

Proposed Diagnosis

T-cell lymphoproliferative disease with putative T_{FH} differentiation in the context of chronic immune supression.

Interesting Feature(s)

This is a clonal systemic lymphoproliferation in a patient with a PTEN-hamartoma tumour syndrome. Since lymphomas are scarcely reported in these patients (being mostly B-cell), our case might reasonably be ascribed to chronic mTOR-pathway inhibition by sirolimus.

It represents an unusual morphological pattern for a T-cell lymphoproliferative disease.

Despite its lack of a proper immunophenotype and typical mutations, certain features point towards a T_{FH}-cell differentiation.

It illustrates the challenging differencial between post-transplant-like neoplasms and *bona fide* lymphomas.

EA4HP24-LYWS-323

Epstein-Barr Virus Positive Iatrogenic Lymphoproliferative Disorder in a Patient with Chronic Refractory Immune Thrombocytopenic Purpura Receiving Immunomodulatory Therapies

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Case Description

This 79-year-old female with history of breast cancer status post chemotherapy and radiation, and chronic refractory immune thrombocytopenic purpura (ITP) complicated by intracranial hemorrhage and gastrointestinal bleeding, presented with a one month history of fatigue and weight loss (30 lb/13.6 kg), and underwent a lymph node biopsy for lymphadenopathy. At presentation she was receiving romiplostim and prednisone. She had received many previous therapies for ITP including rituximab, fostamatinib, mycophenolate mofetil, azathioprine, cyclosporine A, cyclophosphamide/vincristine, IVIg, Rho(D) Ig, dapsone, corticosteroids, danazol, and eltrombopag. CBC showed WBC: 8.1K/mL[3.4-11.2], Hgb: 9.5g/dL[13.7-17.5], MCV: 89.4fL[80-100], PLT: 208K/mL[150-450].

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections showed architectural effacement by an atypical mixed cell population. The morphology was variable in different areas of the tissue. Large atypical Hodgkin/Reed-Sternberg (HRS)-like cells with multinucleation, prominent nucleoli and abundant cytoplasm were seen, admixed with numerous histiocytes, small lymphocytes, and a variable number of eosinophils. Scattered large atypical cells with a single nucleus and prominent nucleoli were also seen. Some areas consisted of more large atypical cells and fewer histiocytes and eosinophils. Scattered mummified cells and apoptotic cells were seen. Additionally, in some areas the atypical cellular proliferation was separated into nodules by collagen.

Immunophenotype

Immunohistochemical stains showed variable staining patterns. In some areas the large atypical cells showed expression of PAX5 (dim to moderately bright), CD15 (bright) and CD30, and were negative for CD20. EBER (EBV) was positive. In other areas, EBER positive cells ranged in size and expressed CD20 (bright), CD15 (variable), CD30 (variable bright), and PAX5 (variable). A subset of the large cells expressed BCL2, BCL6 and MUM1. The EBER

positive cells were variably LMP1 positive. The proliferation rate (Ki-67) was variable (10-70%) in different areas.

Cytogenetics

A complex karyotype was observed with t(4;7), der(6)t(6;12), and additional material on 3q, 10q, 12q, 15p, 19q and 22p, in 13/20 metaphase cells. FISH did not identify *BCL6, MYC, MYC::IGH*, or *IGH::BCL2* gene rearrangements.

Molecular Studies

DNA extracted from FFPE/fresh tissue showed a clonal rearrangement in a polyclonal background (*IGK*), polyclonality (*IGH*-FR3) and a weak clone in a polyclonal background (*TRG*).

Proposed Diagnosis

Polymorphic lymphoproliferative disorder, EBV positive, iatrogenic immunosuppression (WHO5); iatrogenic immunosuppression associated polymorphic lymphoproliferative disorder (ICC)

Interesting Feature(s)

The biopsy showed heterogeneity which was diagnostically challenging. Features suggestive of classic Hodgkin lymphoma (CHL) with EBV+ HRS-like cells were seen. EBV-positive cells of variable size which variably expressed B-cell markers were also seen. CHL with progression to a diffuse pattern with increased CD20 expression was considered. However, the BCL6 expression is unusual (~5%) in CHL. In the setting of chronic refractory ITP, treated with various immunomodulatory and immunosuppressive therapies, a polymorphic lymphoproliferative disorder arising in immune deficiency/dysregulation was favored particularly in light of the CD20 expression, albeit variable, and the clonal B cell population identified by PCR analysis. The immunodeficiency could also be attributed to the patient's age.

EA4HP24-LYWS-330

Infectious mononucleosis complicated with spontaneous splenic rupture and a clonal CD8+ T-cell lymphoproliferation mimicking a T-cell lymphoma.

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Case Description

A 34-year-old man presented to his local doctor with fever and upper respiratory symptoms. He was prescribed anti-fever drugs. Days later he presented to the hospital with acute abdominal pain. The physical examination revealed hepatosplenomegaly with spontaneous spleen rupture. A splenectomy was performed and a liver biopsy was taken.

The spleen weight 727g. We received the case in consultation with the presumptive diagnosis of PTCL, NOS vs a hepatosplenic T-cell lymphoma.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

not available

Details of Microscopic Findings

The spleen showed an area of subcapsular hemorrhage most probably the rupture site. Histologically, the white pulp was atrophic, and the red pulp was expanded. The red pulp was infiltrated by a polymorphic infiltrate with small, medium and large lymphoid cells. The larger cells showed irregular nuclei with prominent nucleoli and abundant cytoplasm. The liver biopsy showed normal architecture; however, there was a dense lymphoid infiltrate both in the portal spaces and intrasinusoidal. The cells in the liver were more medium-sized with mature chromatin and scant cytoplasm. The hepatocytes show mild cholestasis and focally there was central necrosis with granulocytes.

Immunophenotype

The infiltrating cells both in spleen and liver were positive for CD3, CD5, CD8, TIA1, granzyme B and Beta-F1 (TCR alfa-beta), MIB1 demonstrates a relatively high proliferation rate. The cells are negative for CD4, CD56 and mostly negative for GATA3 and TBX1. CD20 is positive in the B-cells in the residual atrophic white pulp. EBER in situ hybridization demonstrate many scattered positive cells. LMP1 was positive in few cells and EBNA 2 was negative. The double stains for EBER/CD3, EBER/CD8 and EBER/CD20 show that the EBER positive cells are the CD20+ B-cells.

Cytogenetics

not performed

Molecular Studies

TCRB-C (Biomed): a clonal peak of 188bp

TCRG (Biomed): Two clonal products of 190 bp and 198 bp in a polyclonal background

Proposed Diagnosis

Acute infectious mononucleosis complicated with splenomegaly and a spontaneous splenic rupture with a clonal CD8+ cytotoxic T-cell lymphoproliferation.

Interesting Feature(s)

The case has several interesting features. 1) the diagnosis of acute infectious mononucleosis (IM) in a young adult patient that was missed and complicated with a splenic rupture. Splenic spontaneous rupture has been reported occasionally as the presenting event in IM, and up to 15% of splenic ruptures are attributed to IM. 2) The diagnosis in these cases is challenging since, as in this case, the morphology may strongly suggest a malignant lymphoproliferation, including the demonstration of a clonal CD8+ T-cell proliferation. 3) the age of the patient was also misleading since most cases of IM are seen in the adolescence. The patient recovered uneventfully after the surgery and he is completely asymptomatic. 4) In this case the infected EBER cells, was the clue to the diagnosis, clearly demonstrating that the identification of the EBER infected cells is of utmost importance. The lack of EBNA2 expression (Latency 2) suggested a late stage of EBV acute infection. 5)

During acute IM it is not rare that isolated EBER+ CD8+ T-cells are identified. The meaning of this for future development of EBV+ T-cell LPDs is not known.

EA4HP24-LYWS-359

EBV(+) large B-cell lymphoma of the brain in the setting of immuno-suppressive medication

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Case Description

The patient is a 59-year-old female with a history of undifferentiated connective tissue disease, receiving mycophenolate and hydroxychloroquine. In addition, she has a history of liver cirrhosis secondary to her underlying metabolic disease, hypertension, hypothyroidism, diabetes, and diabetic neuropathy. She presented to the emergency department with worsening left lower extremity weakness over several weeks. Magnetic resonance imaging (MRI) revealed a right ring-enhancing mass. Neurosurgery was consulted, and a stereotactic biopsy was performed.

Biopsy Fixation Details

Small fragments of brain biopsy were fixed in formalin.

Frozen Tissue Available

No

Details of Microscopic Findings

Brain biopsy: Sections show small fragments of brain tissue with an infiltrate of large atypical lymphoid cells with irregular nuclei, stippled chromatin, and moderate amounts of cytoplasm.

Immunophenotype

Immunohistochemistry: The infiltrate was composed of large atypical CD20(+) B cells, which were positive for CD30, PAX-5, BCL2, BCL6, and MUM-1; and negative for CD3, CD10, and Cyclin D1. EBER in-situ hybridization highlighted numerous EBV-infected cells. Ki-67 demonstrated a proliferation index of 60%.

Cytogenetics

Not performed due to the paucity of the tissue.

Molecular Studies

Not performed.

Proposed Diagnosis

Large B-cell lymphoma, EBV(+), in the setting of immuno-suppressive medication (WHO 5th edition online beta version) / Iatrogenic immunodeficiency-associated lymphoproliferative disorder, large B-cell lymphoma, EBV(+) (International Consensus Classification 2022)

Interesting Feature(s)

- Lymphoid proliferations in the setting of immune deficiency and immune dysregulation (IDD) are typically seen in patients with HIV, post-transplant, as well as in some rheumatologic conditions treated with methotrexate.
- It is unclear whether Hans algorithm or other immunophenotypic algorithms adequately risk-stratify patients in this clinical setting. The frequency and prognostic/theragnostic impact of CD30 staining in this setting is largely unexplored.
- This case is unusual, given its initial presentation as a brain mass in a patient with a history of undifferentiated connective tissue disorder treated with mycophenolate and hydroxychloroquine.

EA4HP24-LYWS-363

Diffuse Large B-cell Lymphoma Associated with Chronic Inflammation

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Case Description

A 53-year-old male with a long history of tobacco dependence and chronic obstructive pulmonary disease presented with progressive left-sided neck and upper back pain for three months. A CT scan at presentation showed large loculated left-sided pleural effusion and emphysematous changes. Thoracentesis showed purulent fluid with low glucose, consistent with empyema. Pleural fluid cytology revealed no atypical/ malignant cells. The patient was managed with antibiotics and chest tube insertion with transient improvement. Imaging two months later revealed recurrent loculated left pleural effusion and additional pleural thickening and enhancement, compatible with subacute/ chronic pyothorax. The fibrotic pleura with lung entrapment led to thoracotomy with left pulmonary decortication and pneumolysis.

Biopsy Fixation Details

10% Neutral Buffered Formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

Histologic sections reveal thickened pleural peels with clusters of large atypical lymphocytes in a sclerotic background. The large atypical lymphoid cells with round to irregular nuclear contours, occasional prominent nucleoli, and scant cytoplasm are appreciated within dense fibrous background imparting mechanical artifact. Occasional

apoptotic bodies are noted. The background tissue also revealed clusters of bland foamy histiocytes, areas with chronic inflammation rich in lymphoplasmacytic cells, and foci with lymphoid follicles.

Immunophenotype

By immunohistochemistry the atypical lymphoid cells were positive for CD30, PAX5 (predominantly positive), CD20 (rare cells, weak), CD79a (predominant), MUM-1 (partial), CD138 (rare, weak), p53 (rare, strong) and EBV-LMP1 (occasional cells) and were negative for HHV-8, CD15, CK AE1/3, CD3, ALK, kappa and lambda. Ki-67 highlights ~90% of the atypical cells. The atypical cells are uniformly positive for EBER by in situ hybridization. CD163 highlights the background histiocytes. All controls stained appropriately.

Cytogenetics

FISH studies for *BCL2, BCL6*, and *MYC* are pending.

Molecular Studies

Comprehensive next-generation targeted sequencing is pending.

Proposed Diagnosis

Diffuse large B-cell lymphoma associated with chronic inflammation

Interesting Feature(s)

While the majority of diffuse large B-cell lymphoma associated with chronic inflammation (CI-DLBCL) cases present with a large mass, our patient was discovered to have thickened pleura with enhancement on CT scan.

Importantly, our case presented with sudden onset pain in the neck and upper back with pneumothorax. Pain in the setting of chronic pyothorax has been described as a sign of malignancy, not a common feature of chronic pyothorax. Fibrosis of the pleura with lung entrapment over the next few months was compatible with subacute/ chronic empyema and required surgical decortication. These clinical manifestations were essential in diagnosis, especially to exclude the possibility of a rare fibrin-associated large B-cell lymphoma, which presents incidentally without significant symptoms.

While CI-DLBCL may occur at various sites, pleural involvement has frequently been seen in the setting of pleuropulmonary tuberculosis requiring artificial pneumothorax. Our case represents a rare presentation with chronic empyema.

Our case shows an activated B-cell profile with LMP1 and EBER expression, highlighting the EBV-driven etiology.

The presence of p53 overexpressing lymphoma cells is intriguing and requires correlation with *TP53* mutational status (pending molecular testing).

EA4HP24-LYWS-375

EBV-positive B-cell lymphoproliferation in mesenteric lymph nodes of a patient with colorectal adenocarcinoma pretreated with anti-PD1 (Pembrolizumab)

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Case Description

01/2023: Diagnosis of coecal adenocarcinoma in an 84-year-old female patient, stage cT4b cN1 M1, deficient mismatch repair.

01-07/2023: Pembrolizumab

04/23: Partial remission

06/23: Palliative resection of a mucinous adenocarcinoma, stage ypT3c pN0. Enlarged lymph nodes with suspicious infiltrate submitted for consultation.

12/23: Complete remission

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Mesenteric lymph node with partially effaced architecture due to a polymorphous infiltrate. Most cells exhibited small to medium-sized round nuclei with coarse chromatin and scant occasionally basophilic cytoplasm. Dispersed within this background occasional large cells mostly with features of immunoblasts or Hodgkin- and Reed-Sternberg-like (HRS) cells were present accompanied by some histiocytes, occasional eosinophils and high endothelial venules.

Immunophenotype

CD20 immunostain disclosed residual follicular B-cell aggregates. The infiltrate expressed CD19, CD79a and IRF4 with variable intensity. Only a proportion showed variable expression of CD20 and PAX5. Most of the cells expressed CD30 with a variable intensity, while only the large cells were CD15 positive. Only few CD138-positive plasma cells were present showing polytypic immunoglobulin light chain expression. Latent Epstein-Barr virus (EBV) infection of most B-cells was detected by EBER-in-situ hybridization. There was no expression of EBV nuclear antigen 2, only the large cells expressed EBV-encoded latent membrane protein-1.

Few lymphocytes expressed the BZLF1 protein of EBV indicative of transition into the lytic infection phase.

Cytogenetics

Not done

Molecular Studies

A B-cell clone was demonstrated by sending institution

Proposed Diagnosis

Polymorphic lymphoproliferative disorder EBV+, associated with immunomodulatory treatment (anti-PD1) for colorectal adenocarcinoma

Interesting Feature(s)

Only single reports on development of clonal lymphoproliferative disorders in association with immune checkpoint inhibitors published

The few lymphoproliferations published are of T-cell-lineage without EBV-association

EA4HP24-LYWS-384

Post-COVID Vaccine Induced Lymphademnopaty

Dr. José L. Solórzano Rendón[2,1], PhD/MD Victoria Menéndez[1], Eva Díaz Martín[1], Prof. Ricardo González-Cámpora[3], Dr. Carlos Montalbán[1], Dr. Giovanna Roncador[4], Dr. Juan F. García[2,1]

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Case Description

A 46-year-old male with no particular disease background, with a history of 6 months of persistent cervical lymphadenopathies; after administration of a COVID vaccine AZD1222 (ChAdOx1-SARS-COV-2, Oxford/AstraZeneca). Lymphadenectomies were performed to make the diagnosis.

Biopsy Fixation Details

H&E and immunohistochemistry (IHC) staining were performed on formalin-fixed, paraffin-embedded (FFPE) tissue from lymph nodes samples. IHC was performed with a heat-induced epitope retrieval buffered by Tris or EDTA at pH 9, with the BOND RX automated stainer system (Leica Biosystems, Buffalo Grove, IL). A panel of primary antibodies was tested using routine diagnostic procedures: CD20, CD3, CD4, CD8, CD30, CD23, PD-1, BCL2, BCL6, CD68, CD33, MNDA, MUM1, CD38, CD123, CD1a and CD85a (produced by Giovanna Roncador mAb unit CNIO).

Frozen Tissue Available

No available

Details of Microscopic Findings

The lymph node biopsies showed an enlarged lymph node with a partial effacement of the architecture, with marked expansion of the paracortical area, resembling a lymphoproliferative process, like angioimmunoblastic T-cell lymphoma (AILT).

Immunophenotype

The IHC highlighted an expansion of the paracortical area due to myeloid-monocytic cells (CD33+, CD68+). Also exhibit a heterogeneous population of mature T-lymphocytes (CD4+, CD8+) in the interfollicular area and an increase of follicular dendritic cells (CD21+/CD23+) in the neighborhood of the follicles. Germinal centers are recognized well preserved (BCL2+). EBV was negative.

Multiplex Immunofluresce (mIF)

A mIF panel was created to interrogate the distributios of the myeloid cells. The panel include: CD33, CD68, CD11b, CD85a and CD68. mIF assays were done on all LN samples using the Akoya's TSA-Opal Multiplex kit (Akoya Biosciences, Marlborough, MA) according to manufacturer guidelines, and using the BOND RX stainer. Briefly, 5 µm FFPE tissue sections were consecutively incubated with anti-CD33, anti-CD11b, anti-CD85a and anti-CD68 with a previous heat induced epitope retrieval protocol. Each primary Ab was followed by incubation with TSA fluorophores Opal 540, Opal 570, Opal 620 and OPAL 520, respectively, and final nuclear counterstaining with diamidino-2-phenylindole (DAPI). For each antibody, staining parameters were first optimized using single chromogenic IHC and monoplex IF on tonsil and reactive lymph node sections.The mIF highlighted the expansion of granulocytic myeloid cells (g-MDC) and monocytic myeloid cells (m-MDC) in the paracortical areas.

Cytogenetics

No performed.

Molecular Studies

PCR clonality assays showed polyclonally rearranged IGH and TCR genes in all samples, consistent with reactive lymphoproliferations.

Proposed Diagnosis

Myeloid paracortical expansion in post-vaccine lymphadenitis.

Interesting Feature(s)

A high incidence of COVID-19 vaccine-induced lymphadenopathies have been described and could be an important problem in cancer imaging diagnostic dilemma.

DNA or RNA vaccination could induce lymphadenitis due to the activation of an innate immunity by engaging myeloid cells, M-MDCs, CD14+ innate monocyte memory, and CD16+ monocytes that can play different role in protection.

The feature of these histological finding is still not well annotated, probably for the unusual clinical presentation and the lack of the technology to interrogate the myeloid compartment.

Here we describe a case with a comprehensive phenotyping identified a characteristic expansion of immature myeloid cells (MDCs), both from granulocytic (gMDCs) and monocytic (mMDCs) derivation consistent with an innate immune response.

EA4HP24-LYWS-388

A transformed lymphoma or another lymphoma associated with IDD?

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Case Description

A 71-year-old male was presented with generalized lymphadenopathy in January of 2024. He had a Lymph node biopsy in the outside hospital indicated follicular lymphoma, grade 2 on April of 2016 and EBER was negative. Then the patient underwent 5 cycles of CHOP regimen chemotherapy. Another lymph node biopsy in 2022 revealed DLBCL (non-GCB) with Epstein-Barr virus (EBV) infection. In 2024, the third lymph node biopsy showed follicular lymphoma 3A along with plasmacytoid differentiation, EBV infection and in situ follicular neoplasm. Unfortunately, EBV DNA copies were unavailable during his stay in hospital. Whether the second or the third sample is indeed a transformed lymphoma or another lymphoma associated with IDD?

Biopsy Fixation Details

No details

Frozen Tissue Available

No

Details of Microscopic Findings

Findings were shown in the PDF file.

Immunophenotype

Three biopsies showed different immunophenotype as shown in the PDF.

Cytogenetics

No

Molecular Studies

The two tissue specimens from 2022 and 2024 showed the same peak in the IG clone rearrangements.

Proposed Diagnosis

Three biopsies showed different diagnosis. Whether the second or the third sample is indeed a transformed lymphoma or another lymphoma associated with IDD?

Interesting Feature(s)

1. There was no EBER staining in the first biopsy. However, the number of EBER positive cells increased after the treatment.
2. The two tissue specimens from 2022 and 2024 showed the same peak in the IG clone rearrangements, which indicated they are clone related.
3. The second biopsy showed Non-GCB subtype instead of GCB though the first biopsy indicated FL.
4. The third biopsy showed complicated morphological change and was diagnosed as

follicular lymphoma 3A along with plasmacytoid differentiation, EBV infection and in situ follicular neoplasm .

EA4HP24-LYWS-409

T-lymphoblastic lymphoma/leukemia in the setting of germline SMARCA4 mutation, prior cytotoxic chemotherapy and EZH2 inhibitor.

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Case Description

In 2017, a 38-year-old female with a germline SMARCA4 pathogenic variant (X668_splice) developed small cell carcinoma of the ovary, hypercalcemic type, featuring a somatic SMARCA4 mutation (X953_splice). Initial intervention involved an exploratory laparotomy with left salpingo-oophorectomy, followed by adjuvant etoposide/cisplatin. Subsequently, disease recurrence prompted another exploratory laparotomy, involving tumor debulking, total abdominal hysterectomy (TAH), and right salpingo-oophorectomy in 2019.

In the face of disease progression, the patient underwent multiple lines of therapy, encompassing cisplatin, doxorubicin, atezolizumab, paclitaxel, ipilimumab and nivolumab. In 2020, the patient was started on tazemetostat, an EZH2 inhibitor, to which the patient exhibited an excellent response.

However, in 2023, a PET/CT scan revealed hypermetabolic lymphadenopathy both above and below the diaphragm and diffuse FDG uptake throughout the bone marrow. Consequently, the patient underwent left neck mass and bone marrow biopsies.

Biopsy Fixation Details

10% formalin; additionally, decalcification for the bone marrow biopsy

Frozen Tissue Available

N/A

Details of Microscopic Findings

Left neck mass biopsy with a diffuse proliferation of intermediate sized blasts infiltrating fibroadipose tissue.

Bone marrow biopsy with a hypercellular marrow demonstrating an expanded population of variably sized blasts with agranular cytoplasm. Maturing trilineage hematopoiesis present without overt dysplasia.

Immunophenotype

The blasts express CD1a (partial), CD2 (dim), cytoplasmic CD3, CD4, CD5 (dim), CD7 (bright), CD8 (dim), CD10, CD45 (dim), CD48 (dim), CD99 (bright) and TdT; do not express surface

CD3, CD13/CD33, CD16, CD19, CD20, CD34, CD56, CD117, PAX5 and MPO. Pan-cytokeratin is negative. BRG1 (SMARCA4) and BRM (SMARCA2) expression is retained.

Cytogenetics

Normal karyotype.

FISH analysis – No rearrangements or deletions; however, multiple gains detected (full list included in PowerPoint).

Molecular Studies

Fragment analysis – Clonal rearrangements involving TCR Beta and TCR Gamma genes detected.

NGS matched analysis (IMPACT Heme) - 15 somatic mutations, including NOTCH1 (full list included in PowerPoint), and 1 structural variant, SOCS1 deletion. No somatic SMARCA4 or EZH2 mutations detected.

RNA-based NGS analysis (Archer Heme) – No fusions detected.

Proposed Diagnosis

T-lymphoblastic lymphoma/leukemia in the setting of germline SMARCA4 mutation, prior cytotoxic chemotherapy and EZH2 inhibitor.

Interesting Feature(s)

This case raises the possibility of a role of either germline SMARCA4 pathogenic variant or prior cytotoxic chemotherapy or EZH2 inhibitor therapy, or all these factors in the development of T-ALL.

- SMARCA4 mutation and development of T-ALL

SMARCA4 mutations have been reported in approximately 3% of T-ALL (Andrades A, *et al.*). However, no association of germline SMARCA4 alterations with T-ALL is reported in the literature. A recent single case of T-ALL in a 3-year-old with germline SMARCA4 also harbored a germline EZH2 variant (Tibout P, *et al.*).

- Prior cytotoxic chemotherapy and development of T-ALL

There is no established association of prior cytotoxic chemotherapy with T-ALL.

- Prior EZH2 inhibitor therapy and development of T-ALL

Rare cases of T-ALL in association with EZH2 inhibitor have been reported (Morin RD, *et al.*). The temporal association of EZH2 inhibitor with T-ALL in our patient may suggest it's possible role in T-ALL development and warrants further investigation.

EA4HP24-LYWS-453

Polymorphic lymphoproliferative disorder, EBV-positive in the context of iatrogenic immunosupression

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Case Description

This case presents a 67-year-old women with a previous history of dermatomyositis, with cutaneous, pulmonary and oesophageal involvement at the time of diagnosis. Since 2014, the patient was continuously submitted to various courses of different immunosuppressor agents (including cyclophosphamide, azathioprine, methotrexate, rituximab and cyclosporine). Due to the fear of iatrogenic induced complications, azathioprine was stopped in September of 2023. Maintenance therapy with deflazacort was continued.

After the cessation of azathioprine, the patient presented with a solitary cutaneous lesion on the right hemithorax. The lesion was biopsied, submitted to pathologic examination, and the diagnosis of lymphomatosis granulomatosis was rendered. This case was reviewed, and considering the clinical context, the diagnosis was polymorphic lymphoproliferative disorder, lymphomatoid granulomatosis- like pattern, EBV-positive (in the context of iatrogenic immunosuppression).

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

No tissue available.

Details of Microscopic Findings

Skin biopsy: heterogeneous proliferation of cells involving all the cutaneous layers, in a perivascular pattern with angio-destruction and associated foci of necrosis. The proliferation is composed of large B cells with prominent nucleoli, in a background of predominantly small T lymphocytes. Rarely, large T lymphocytes were identified.

Immunophenotype

Large B cells express CD20+, CD3-, PAX5 (weak), CD30+, MUM1+ and EBER+.

Large T cells express CD3+ and TIA1+.

Cytogenetics

Not performed.

Molecular Studies

EBER-ISH positive in the large B cells.

Proposed Diagnosis

Polymorphic lymphoproliferative disorder, lymphomatoid granulomatosis-like pattern, EBV-positive (in the context of iatrogenic immunosuppression).

Interesting Feature(s)

1 - The impact of the clinical context on the final diagnosis.

2 – Are the multiple drug changes of immune supressing agents a predisposing factor for the development of polymorphic lymphoproliferative disorders?
3 – Which was the causing agent?
4 – How long after cessation of an immunosuppressor agent, its effect is a contribution for this diagnosis?

EA4HP24-LYWS-473

Atypical PD1+ CD8 cell proliferation after the treatment of Everolimus and a relative remote exposure to Pembrolizumab

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Case Description
The patient is a 79 yo man with a history of a low grade B cell lymphoma (CLL) received BR and then Ibrutinib in 2017. He developed more prominent axillary and mediastinal lymphadenopathy, which upon biopsy revealed a composite lymphoma comprising classic Hodgkin lymphoma and low grade B cell lymphoma in 2019. His lymphoma progressed and showed refractory to multiple lines of treatment, including EPOCH (2019), Pembrolizumab (2020), Dacarbazine/Bretuximab (2020-2021), Bendamustine (2021), and Obinutuzumab (2021). The lymphadenopathy progressed with new splenic lesions emerged and he developed intermitted fever and night sweats. He was started on Everolimus (MTOR inhibitor) in Jan 2022. Patient shortly developed marked pancytopenia (WBC 3.56, Hgb 3.7, and plt 16), dyspnea and peripheral edema. Everolimus was discontinued. Bone marrow biopsy revealed no evidence of lymphomatous infiltrate. His ferritin level rose from 1442 to 9800 ng/mL in 2 weeks. Serum soluble IL2 receptor (Feb 2022) reached 68225 pg/mL. He complained of abdominal fullness with dyspnea on exertion and orthopnea, managed for high output cardiac failure from acute on chronic anemia. A paracentesis for a mild ascites drained 600 ml fluid. Patient expired shortly after hospice elected.
Biopsy Fixation Details
Cytology preparation of peritoneal fluid was done. Cytospin smears with pap stain and diff quick stain were prepared. A cell block was made using plasma thrombin method, followed by 10% buffered formalin fixation and paraffin embedding.
Frozen Tissue Available
N/A
Details of Microscopic Findings
Both smears and cell block showed lymphocyte dominant population. The lymphocytes in cell block were small to intermediate size with irregular nuclei and minimal cytoplasm.

Frequent mitotic figures and apoptotic bodies were noted. Occasional large atypical lymphocytes were noted with variably abundant amount of cytoplasm.

Immunophenotype

Immunostains showed that the lymphocytes were overwhelmingly represented by CD8 T cells with no significant CD20 B cells present. A minor component CD4 T cells were present. There were rare scattered CD30 positive cells noted, which were negative for CD20 and CD15, positive for Pax5, MUM1, BCL6 (weak) and CD79a, most compatible with immunoblasts. The CD8 cells showed loss of CD5 and express CD3, CD2, CD7, PD1, TCR-betaF1, granzyme B. They were negative for GATA3 and CD10. ISH for EBV was negative. A high proliferation rate of >85% was noted by ki-67.

Cytogenetics

N/A

Molecular Studies

TCR-gamma gene rearrangement reported clonal.

Proposed Diagnosis

Atypical PD1 positive CD8 T lymphocytosis after Everolimus and a relatively remote history of Pembrolizumab.

Interesting Feature(s)

The atypical PD1 CD8 cell proliferation occurred in a clinical setting of hemophagocytic lymphohistiocytosis (HLH) (fever, splenomegaly, pancytopenia, ferriinemia, and elevated solular IL2 receptor). Though the atypical CD8 cells are highly proliferative by Ki-67, the degree of atypical infiltrate caused only mild ascites. PD1+ CD8 cell proliferation has been reported in patient receiving immunotherapy such as Pembrolizumab. However, the exposure to Pembro in this patient was over a year ago. Moreover, the onset of constellation of symptoms occurred shortly after the start of Everolimus. Neither HLH nor PD1+ CD8 cell proliferation have been reported to be associated with Everolimus treatment.

EA4HP24-LYWS-474

Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphoma involving the liver, in the setting of autoimmune hepatitis treated with azathioprine

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Case Description

Patient history and clinical course: 75-year-old female with history of autoimmune hepatitis (for 10 years) treated with azathioprine (~3-5 years) with decompensated liver cirrhosis complicated by portal hypertension with recurrent ascites, esophageal varices and recurrent hematemesis. She was found to have a right liver lobe mass measuring 3.4 cm

on serial abdominal ultrasound performed for hepatocellular carcinoma screening that was biopsied 4 months later. Staging PET/CT showed right middle lung lobe nodule, mediastinal lymphadenopathy and bone lesions in L4 and L5. Ascites fluid cytology was negative for malignancy. The azathioprine was discontinued after the diagnosis of lymphoma. She was not considered a candidate for chemotherapy due to significant comorbidities. Her condition continued deteriorating and she died of hemorrhagic shock due to upper gastrointestinal bleeding approximately 1 month after diagnosis of lymphoma.

Biopsy Fixation Details

Formalin fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections demonstrate large areas of necrosis, and few viable areas show a relatively diffuse infiltrate of large sized lymphoid cells with irregular nuclear contours, dispersed chromatin and variably prominent nucleoli. Scattered mitoses and apoptotic bodies are seen. Background liver showed centrilobular sinusoidal dilatation, bridging fibrosis and portal lymphoplasmacytic inflammation, consistent with treated autoimmune hepatitis.

Immunophenotype

The lymphoma cells were positive for CD20, EBER-CISH (>80%), EBV-LMP1, CD45, CD10 (dim subset >30%), MUM1, BCL6 and are negative for EBNA 2, cyclin D1, TdT, CD3 and CD5. BCL2 expression is seen in less than 50% of the cells. MYC expression is seen on ~20% of the cells. Ki-67 is positive in ~ 60% of the nuclei in the viable areas. Cytokeratin AE1/AE3 highlights the residual epithelium. CD3 highlights scattered positive background T cells.

Cytogenetics

Fluorescence in situ hybridization (FISH) studies are negative for *MYC*, *BCL2* and *BCL6* gene rearrangements.

Molecular Studies

Lymphoid NGS panel performed showed a mutation in ***TP53*** p.Arg248Pro (VAF 31%). Copy number losses in chromosome 11q (11q21-q22.3) involving the *ATM* region and involving the X chromosome (Xp22.33-q28) were also detected.Tumor mutational burden (TMB) was low (4.7 mutations/MB).

Proposed Diagnosis

Iatrogenic immunodeficiency-associated lymphoproliferative disorder - EBV positive (ICC 2022 and WHO 2016)/ Diffuse large B-cell lymphoma, EBV-positive, in the setting of immunosuppressive therapy (WHO 2022).

Interesting Feature(s)

EBV-positive DLBCL involving the liver in the setting of autoimmune hepatitis treated with azathioprine.

Panel Diagnosis Session III

Panel Diagnosis: Immunosuppressive/Immunomodulatory associated LPD: B-cell lineage, polymorphic

Case	Panel Diagnosis
EA4HP24-LYWS-87	WHO5: EBV+ Mucocutaneous ulcer, immunosuppressive related (steroids and vidolivumab) ICC: Iatrogenic lymphoproliferative disorder, EBV+ polymorphic B-cell type
EA4HP24-LYWS-323	WHO5: Polymorphic lymphoproliferative disorder, EBV+, iatrogenic immunosuppression/immunomodulation-ITP ICC: Iatrogenic lymphoproliferative disorder, EBV+ polymorphic B-cell type
EA4HP24-LYWS-453	WHO5: Polymorphic lymphoproliferative disorder, EBV+, iatrogenic immunosuppression, dermatomyositis, multiple treatments ICC: Iatrogenic lymphoproliferative disorder, EBV+ polymorphic B-cell type

Panel Diagnosis: Immunosuppressive/Immunomodulatory associated LPD: B-cell lineage, monomorphic

Case	Panel Diagnosis
EA4HP24-LYWS-379	WHO5: Classic Hodgkin lymphoma, EBV+, immunomodulator therapy ICC: Classic Hodgkin lymphoma, EBV+ (likely iatrogenic after immunomodulator therapy)
EA4HP24-LYWS-234	WHO5: Extranodal marginal zone lymphoma (with background EBV reactivation) ICC: Extranodal marginal zone lymphoma (with background EBV reactivation)
EA4HP24-LYWS-359	WHO5: Diffuse large B-cell lymphoma, EBV+, immunosuppressive therapy ICC: Iatrogenic immunodeficiency-associated LPD, EBV+ diffuse large B-cell type
EA4HP24-LYWS-388	Unable to fully classify from available material
EA4HP24-LYWS-474	WHO5: Diffuse large B-cell lymphoma, EBV+, immunosuppressive therapy ICC: Iatrogenic immunodeficiency-associated LPD, EBV+ diffuse large B-cell type

Panel Diagnosis: Immunosuppressive/Immunomodulatory associated LPD: T-cell lineage

Case	Panel Diagnosis
EA4HP24-LYWS-193	Atypical lymphoproliferative disorder of non-canonical Tfh cells
EA4HP24-LYWS-124	1. DLBCL, EBV+, iatrogenic setting (WHO5) / Iatrogenic immunodeficiency-related LPD, EBV+, DLBCL type (ICC) 2. Peripheral T-cell lymphoma NOS (WHO5 and ICC)
EA4HP24-LYWS-287	WHO5: NK-large granular lymphocyte leukemia, iatrogenic setting ICC: Chronic LPD of NK-cells
EA4HP24-LYWS-473	Atypical clonal T-cell proliferation

Panel Diagnosis: Interventions associated with solid tumors

Case	Panel Diagnosis
EA4HP24-LYWS-23	WHO5: Nodal T Follicular Helper Cell Lymphoma, NOS, iatrogenic setting, chemotherapy and anti-EGFR inhibitor ICC: Follicular helper T-cell lymphoma, NOS
EA4HP24-LYWS-173	WHO5: Polymorphic lymphoproliferative disorder, EBV+, iatrogenic, chemotherapy-esophageal carcinoma ICC: Iatrogenic lymphoproliferative disorder, EBV+, polymorphic B-cell type
EA4HP24-LYWS-286	Atypical T-cell proliferation, consistent with subcutaneous panniculitis-like T-cell lymphoma
EA4HP24-LYWS-375	WHO5: Polymorphic B-cell lymphoproliferative disorder, EBV+, pembrolizumab ICC: Iatrogenic lymphoproliferative disorder, EBV+ polymorphic type
EA4HP24-LYWS-423	1) Clonal plasma cells at site of T-VEC injection for melanoma 2) Follicular lymphoma of parotid or intraparotid lymph node

Panel Diagnosis: DRESS Syndrome

Case	Panel Diagnosis
EA4HP24-LYWS-208	Reactive lymphoid proliferation, consistent with DRESS syndrome
EA4HP24-LYWS-32	Reactive lymphoid proliferation, consistent with DRESS syndrome in appropriate clinical setting
EA4HP24-LYWS-86	Reactive lymphoid proliferation, consistent with DRESS syndrome in appropriate clinical setting

EA4HP24-LYWS-107	Reactive lymphoid proliferation, consistent with DRESS syndrome in appropriate clinical setting
EA4HP24-LYWS-203	Reactive lymphoid proliferation, consistent with DRESS syndrome in appropriate clinical setting
EA4HP24-LYWS-297	Reactive lymphoid proliferation, consistent with DRESS syndrome

Panel Diagnosis: CAR T-cell therapy associated complications

Case	Panel Diagnosis
EA4HP24-LYWS-262	Dedifferentiated transformed follicular lymphoma following CAR T-cell therapy
EA4HP24-LYWS-172	EBV+ T-cell lymphoma following CAR-T cell therapy for EBV+ DLBCL, NOS
EA4HP24-LYWS-88	Initial: B-lymphoblastic leukemia with atypical histiocytic infiltrate after immunotherapy Subsequent: Transdifferentiation of B-lymphoblastic leukemia to histiocytic sarcoma following CAR-T cell therapy
EA4HP24-LYWS-93	Atypical T-cell proliferation, delayed CAR T-cell response? (not proven that they are not CAR T-cells)
EA4HP24-LYWS-186	Reactive proliferation of CAR T-cells with hyperleukocytosis and cerebrospinal fluid infiltration. GI tract mucosa with immune mediated injury pattern and markedly reduced to absent plasma cells

Panel Diagnosis: Complications in CLL treated with Bruton tyrosine kinase inhibitors

Case	Panel Diagnosis
EA4HP24-LYWS-26	CLL with pseudo-Richter transformation consistent with recent interruption of ibrutinib
EA4HP24-LYWS-90 (1)	CLL/SLL with pseudo-Richter transformation following BTK-inhibitor withdrawal
EA4HP24-LYWS-90(2)	CLL/SLL with pseudo-Richter transformation following BTK-inhibitor withdrawal
EA4HP24-LYWS-97	SLL/CLL with early pseudo-Richter change following BTK-inhibitor withdrawal
EA4HP24-LYWS-218	SLL/CLL with pseudo-Richter transformation following BTK-inhibitor withdrawal
EA4HP24-LYWS-221	SLL/CLL with pseudo-Richter transformation in the context of temporal acalabrutinib interruption
EA4HP24-LYWS-17	Anaplastic large cell lymphoma, ALK negative arising in BTK-inhibitor therapy for SLL/CL

Panel Diagnosis: Dasatinib-associated lymphadenopathy

Case	Panel Diagnosis
EA4HP24-LYWS-226	Follicular hyperplasia, Dasatinib-associated and focal polymorphic lymphoproliferative disorder, EBV-positive
EA4HP24-LYWS-291	Paracortical hyperplasia, Dasatinib-associated
EA4HP24-LYWS-188	Pediatric type follicular lymphoma

Panel Diagnosis: COVID-19 vaccination associated lymphadenopathy

Case	Panel Diagnosis
EA4HP24-LYWS-18	Follicular hyperplasia with light chain-restricted germinal centers and extrafollicular activation, post COVID-19 mRNA vaccine
EA4HP24-LYWS-85	Extrafollicular activation, post COVID-19 mRNA vaccine
EA4HP24-LYWS-149	EBV reactivation with necrosis, post COVID-19 vaccine with DRESS syndrome
EA4HP24-LYWS-384	Hyperplasia of marginal zones, paracortical hyperplasia with immature myeloid cells, post COVID-19 viral recombinant vaccine

Panel Diagnosis: Miscellaneous

Case	Panel Diagnosis
EA4HP24-LYWS-72	Reactive lymphoid hyperplasia of the uterine cervix
EA4HP24-LYWS-138	Lymphoma, EBV-positive, unable to further classify, HIV-setting

LYMPHOMA SESSION IV:
Indolent paediatric lymphomas

Oral Presentations

EA4HP24-LYWS-121	Atypical Lymphoid Proliferation Mimicking Pediatric Nodal Marginal Zone Lymphoma
EA4HP24-LYWS-202	A case with hybridizing features between pediatric-type follicular lymphoma (PTFL) and pediatric nodal marginal zone lymphoma (PNMZL)
EA4HP24-LYWS-430	Follicular lymphoma, pediatric type, in a lymph node in the neck
EA4HP24-LYWS-371	Extramedullary plasmacytoma in a child

EA4HP24-LYWS-121

Atypical Lymphoid Proliferation Mimicking Pediatric Nodal Marginal Zone Lymphoma

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Case Description

A 22-year-old female with no significant past medical history and no recent history of infection, presented with a left-sided pre-auricular mass that was well-circumscribed, mobile, and measured approximately 2cm. CT showed a homogenously hyperdense mass, 2.2 x 2.0 x 1.1 cm, arising along the anterior margin of the superficial lobe of the parotid gland. The patient underwent a left parotidectomy with facial nerve dissection.

Biopsy Fixation Details

The specimen measuring 2.2 x 1.7 x 1.0 cm was received in 10% neutral buffered formalin. Sectioning of the specimen demonstrated solid, homogenous, pink-tan, glistening cut surfaces. The outer surface showed residual salivary gland tissue. The entire specimen was submitted for histology.

Frozen Tissue Available

No tissue was frozen.

Details of Microscopic Findings

Microscopic examination showed an enlarged lymph node with a small amount of salivary gland tissue adherent to the outer aspect of the capsule. The nodal architecture was mostly obliterated by a vaguely nodular proliferation of small lymphocytes and small and large, fragmented aggregates of germinal center cells. The appearance of the large cellular nodules was reminiscent of progressive transformation of germinal centers (PTGCs). There were pale bands of lymphoid cells of a range of sizes and with pale cytoplasm, consistent with monocytoid B cells, with admixed histiocytes and occasional large cells, often arrayed around the periphery of the cellular nodules, leading to interfollicular compression. Some sections showed preserved lymph node architecture at the periphery.

Immunophenotype

Immunostains showed numerous CD20+ B cells in large, round, oval, or elongated follicles. There were many CD3+ T cells, predominantly in an interfollicular distribution. Germinal center B cells were CD10+, BCL6+, BCL2-, Ki67+. Outside germinal centers, B cells were negative for BCL6 and CD10 and were positive for BCL2, with a Ki-67 proliferation index of about 10%. B cells were encompassed by CD21+ follicular dendritic cell meshworks. A few scattered cells were CD30+, mostly in the pale regions at the periphery of the cellular nodules. Lymphoid cells were negative for cyclin D1. MUM1 stained many loosely clustered cells. With immunohistochemistry and in situ hybridization for kappa and lambda immunoglobulin light chains, there was a significant excess of kappa+ plasmacytoid cells

compared to lambda scattered within nodules of B cells. IgD and IgM-stained small B cells within the large cellular nodules.

Cytogenetics

FISH analysis showed no BCL6, BCL2, or IRF4 rearrangements.

Molecular Studies

B-cell gene rearrangement studies were negative for clonal rearrangement of IGH. Molecular analysis by an NGS panel did not detect any pathogenic mutations.

Proposed Diagnosis

Florid atypical lymphoid proliferation, favor reactive process, mimicking pediatric nodal marginal zone lymphoma

Interesting Feature(s)

Although the clinical, histologic, and immunophenotypic findings together were suspicious for a diagnosis of pediatric nodal marginal zone lymphoma, an indolent lymphoma with an excellent prognosis, the World Health Organization requires a demonstration of clonality, not detected in this case, to establish this diagnosis. Rare cases of lymphadenopathy with atypical lymphoid proliferations related to infectious etiologies (such as Haemophilus influenzae infection) with features mimicking pediatric nodal marginal zone lymphoma have been described. In the absence of a detectable clonal B-cell population and pathogenic mutations, the unusual findings in this case may represent a similar florid, atypical, but reactive process.

EA4HP24-LYWS-202

A case with hybridizing features between pediatric-type follicular lymphoma (PTFL) and pediatric nodal marginal zone lymphoma (PNMZL)

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Case Description

The patient, a 16-year-old boy, presented with an enlarged lymph node measuring 1.5 cm adjacent to the right parotic gland without B symptoms for months. Diagnosis was established on the basis of an excisional biopsy. No systemic treatment was given, and the patient was well after 27 months of watch-and-wait.

Biopsy Fixation Details

Lymph node of the right parotic gland was dissected by surgery and immediately fixed in 10% buffered formalin for more than 12 hours. Tissues were then cut and embedded in paraffin, and serially sectioned. Tissue sections were stained with Hematoxylin-Eosin.

Frozen Tissue Available

No frozen tissue available.

Details of Microscopic Findings

About a half area of the lymph node specimen showed PTFL-like morphological features, whereas the remaining half area showed features compatible with PNMZL.

PTFL-like element featured enlarged follicles, thin or absent mantle zones and serpiginous margin. Tumor cells were blast-appeared, with brisk mitoses, but no prominent nucleoli.

PNMZL-like element featured a small lymphoid cell proliferation that surrounding regressed follicles and expanding into the interfollicular regions, with some follicles showing prominent changes compatible with progressively transformed germinal centers (PTGC).

Immunophenotype

Tumor cells of PTFL components are positive for CD20, CD10, Bcl-6, and negative for Bcl-2. Ki-67 index is about 80-90**%**.

Tumor cells of PNMZL components are positive for CD20, Bcl-2, and negative for CD10, Bcl-6. Ki-67 index is about 30-40**%**.

Cytogenetics

The IGH and IGK rearrangements were positive.

IGH: Tube A (+), Tube B (-), Tube C (-), Tube D (+), Tube E (-);

IGK: Tube A (+), Tube B (+);

IGL: Tube A (-).

Molecular Studies

TNFRSF14, IRF8, MSH6, ADGRV1, MUC16 nonsynonymous SNV were detected by next generation sequencing.

Proposed Diagnosis

Pediatric indolent B cell lymphoma with overlapping features of PTFL and PNMZL.

Interesting Feature(s)

This case showed both PTFL and PNMZL characteristics histologically and immunohistochemically and confirmed that PTFL and PNMZL could occurred at the same time. We have a small series of similar cases with same hybridizing histologic features as the present one, these findings may suggest the possibility that the two diseases are indeed included within a single pediatric B-cell lymphoma entity with broad morphological spectrum.

EA4HP24-LYWS-430

Follicular lymphoma, pediatric type, in a lymph node in the neck

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Case Description

•12 year old male with a singular enlarged (20 mm) lymph node in the neck
•No B-symptoms
•Normal blood work-up
•No comorbidity
•Normal blood and bone marrow (smears, biopsies and flow cytometry)

Biopsy Fixation Details

Formalin-fixed (10%), paraffin-embedded lymph node.

Frozen Tissue Available

No

Details of Microscopic Findings

An enlarged lymph node in the neck with morphological features similar to lymphoid hyperplasia – prominent germinal centers (follicles) with tingible body-macrophages, high germinal center-proliferation (Ki-67), and normal expression of BCL-2 within follicles, but with no apparent zonulation into light or dark zones. Furthermore the lesion showed the ”node within a node”-pattern, with neoplastic follicles ”pushing” residual germinal centers to the periphery of the lymph node.

Immunophenotype

CD20+/CD10+partial/CD5-/kappa+

Cytogenetics

FISH did not show t(14;18).

Molecular Studies

Multiplex PCR showed monoclonal rearrangements of the IgH- and IgK-genes

Proposed Diagnosis

Lymph node in the neck: Follicular lymphoma, pediatric type

Interesting Feature(s)

Follicular lymphoma, pedatric typ, often presents in the head and neck-region as an enlarged lymph node with morphological features that are similar to lymphoid hyperplasia – prominent germinal centers (follicles) with tingible body-macrophages, high germinal center-proliferation (Ki-67), and normal expression of BCL-2 within follicles, but with no apparent zonulation into light or dark zones. Furthermore the lesion often shows the ”node within a node”-pattern, with neoplastic follicles ”pushing” residual germinal centers to the periphery of the lymph node.

The lymphoma is often localized within one lymph node, and often no further treatment than excision of the affected lymph node is needed, which raises the question of whether this entity is a true B-cell lymphoma or a benign clonal B-cell proliferation with excellent prognosis even without any treatment at all.
This case also show-cases the tendency of follicular lymphomas, pediatric type, to show varying degress of, to rather prominent, marginal zone differentiation.

EA4HP24-LYWS-371

Extramedullary plasmacytoma in a child

Prof. Ilske Oschlies[1], Dr. Julia Richter[1], Amelie Alfert[2], Prof. Wolfram Klapper[1]

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Case Description
A 4-year-old male developed severe nasal obstruction with inability to breathe over a period of 3 weeks. The child showed no B-symptoms, normal levels of LDH and beta-2-Microglobulin, no paraprotein in urine or blood, normal leucocyte and thrombocyte count and slight anaemia (Hb 9.7g/dl). Adenoidectomy was performed to remove nasal obstruction. Histopathological examination revealed an infiltration of the pharyngeal tonsil by a mature plasma cell neoplasia. Thorough staging, including bone marrow biopsy and PET-CT, excluded systemic plasma cell neoplasia leading to the diagnosis of extramedullary plasmacytoma. After two years of watchful waiting without any therapy the child is without evidence of disease.
Biopsy Fixation Details
Formalin fixed and paraffin embedded fragmented adenoids
Frozen Tissue Available
no frozen tissue is available
Details of Microscopic Findings
Tonsillar tissue with expansion of interfollicular areas by sheets of mature plasma cells. B-cell follicles are partially attenuated and focal destruction of the tonsillar architecture is detected. Plasma cells replace most of the marginal zone. Occasionally colonization of germinal centres by plasma cells is observed. Focally, the infiltrate of the marginal zone is more polymorphic with an admixture of plasmablastic and plasmacytoid cells.
Immunophenotype
CD20 highlights attenuated B-cell follicles. In the atypical interfollicular compartment only focal CD20 staining.
The plasma cells stain: CD138+, MUM1+, CD20-, Pax5-, IgA+, Lambda +, Kappa-, IgG-, IgM-, IgD-, IgG4-, EBER-, Cyclin D1-, ALK1-, CD56-, Ki67 is variable and is higher within the polymorphic areas.

Cytogenetics

Fluorescence in situ hybridization does not demonstrate any abnormalities associated with plasma cell neoplasias (absence of IGH-break, t(4;14)(p16;q32), t(14;16)(q32;q23), deletion 1p32, gain 1q21, deletion 13q14/*RB1* and deleletion 17p13/*TP53)*.

Molecular Studies

A clonal B-cell receptor-generearrangement was detected. Next generation sequencing (NGS) revealed no mutations in 36 genes commonly involved in lymphomas including *MAP2K*1, *TNFRSF14*, *IRF8* and *TP53*. More extended NGS analysis including sequencing of the *BCR*-gene is currently ongoing and will be presented at the meeting.

Proposed Diagnosis

Extramedullary plasmacytoma (EMP, by WHO and ICC) in a paediatric patient

Interesting Feature(s)

So far less than 10 cases of EMP in children have been reported in the literature (Mann G. et al, Ped. Blood cancer 2007; Vanan I. et al, J Clin Oncol 2009; Shao H. et al; Am. J. Surg. Path. 2010). These cases share localized presentation within the nasopharyngeal area and expression of IGA. The delineation of EMP from extranodal marginal zone lymphoma with plasmacytic differentiation remains to be discussed. EMP represents an example of a localized, clinically indolent extranodal clonal B-cell lymphoproliferation, that may affect children and adolescents. Our case as well as others followed by the German NHL-BFM study group for pediatric patients suggests that this lymphoproliferation may be sufficiently treated by resection only.

Cases Discussed by the Panel

EA4HP24-LYWS-1	Paediatric nodal marginal zone lymphoma of parotid gland and cervical lymph nodes
EA4HP24-LYWS-8	Paediatric primary gastric MALT lymphoma with concomitant high-grade transformation, unusual presentation in adolescent.
EA4HP24-LYWS-13	An unusual pediatric-type follicular lymphoma with marginal zone differentiation
EA4HP24-LYWS-31	Testicular follicular lymphoma in a 30-year-old man
EA4HP24-LYWS-34	A Case of Primary Testicular Follicular Lymphoma in a Young Adult Male
EA4HP24-LYWS-36	Atypical B-cell proliferation with histological and immunophenotypic features of indolent paediatric B-cell lymphoma
EA4HP24-LYWS-40	Pediatric-Type Follicular Lymphoma in a 15-year-old Male
EA4HP24-LYWS-41	Enlarged cervical lymphnode in a young patient.
EA4HP24-LYWS-44	·Atypical proliferation of marginal zone with PTGC (due to polyclonal PCR result) vs pediatric marginal zone lymphoma
EA4HP24-LYWS-63	Pediatric-type follicular lymphoma with extensive marginal zone differentiation
EA4HP24-LYWS-64	Pediatric-type follicular lymphoma presenting as a nasopharyngeal polyp in a 30-year-old female
EA4HP24-LYWS-67	Pediatric-type follicular lymphoma with unusual features
EA4HP24-LYWS-70	A rare case of primary testicular follicular lymphoma in a pediatric patient
EA4HP24-LYWS-95	An Unusual Case of an Enlarging Inguinal Mass in an Adult Man
EA4HP24-LYWS-105	A Challenging Mimicker of Paediatric Nodal Marginal Zone Lymphoma
EA4HP24-LYWS-136	Pediatric type follicular lymphoma in a 39 year old female
EA4HP24-LYWS-150	Ileocecal Mass in a 3yo Male
EA4HP24-LYWS-187	Pediatric-Type Follicular Lymphoma Presenting as a Conjunctival Mass.
EA4HP24-LYWS-209	Pediatric nodal marginal zone lymphoma
EA4HP24-LYWS-254	Plasma Cell Proliferation With Atypical Features in a Pediatric Patient
EA4HP24-LYWS-269	An asymptomatic healthy 8-year-old boy presenting with intramuscular fluctuating mass
EA4HP24-LYWS-304	A lesion of the labia minora in a 13-year old girl
EA4HP24-LYWS-314	Atypical Marginal Zone Hyperplasia in an Adolescent
EA4HP24-LYWS-345	Isolated lymphadenopathy in a young adult
EA4HP24-LYWS-348	Florid nodular lymphoid hyperplasia of the appendix
EA4HP24-LYWS-352	Atypical marginal zone hyperplasia in a child

EA4HP24-LYWS-374	Case of pediatric follicular lymphoma with marginal zone differentiation.
EA4HP24-LYWS-367	A Young Man with a Single Cervical Lymphadenopathy
EA4HP24-LYWS-414	IntestinalLarge B-cell lymphoma withIRF4rearrangement without IRF4 translocation.
EA4HP24-LYWS-422	Early recurrence of a Pediatric Nodal Marginal Zone Lymphoma with a potential clonal evolution.
EA4HP24-LYWS-431	A pediatric-type follicular lymphoma with marked marginal zone differentiation
EA4HP24-LYWS-435	Pediatric-Type Follicular Lymphoma in a Young Male with 10 Years of Follow-up and No Progression
EA4HP24-LYWS-447	Unusual Mutational Profile in Otherwise Typical Pediatric-type Follicular Lymphoma
EA4HP24-LYWS-466	Two pediatric cases of conjunctival atypical follicular hyperplasia with lambda light chain restriction

EA4HP24-LYWS-1

Paediatric nodal marginal zone lymphoma of parotid gland and cervical lymph nodes

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Case Description

A male patient around 10 years of age presented with a several-month history of a right parotid lump. There was no other past medical history of note. FNA and core biopsy samples were taken, then a right total parotidectomy with excision of ipsilateral level II cervical lymph nodes was performed.

Biopsy Fixation Details

All samples were fixed in 10% NBF.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The FNA sample showed features of abnormal germinal centres, suggesting follicular lymphoma, but assessment was challenging due to the dispersed nature of the sample and lack of paired flow cytometry.

Features on the core biopsy were of an atypical follicular proliferation, favouring marginal zone lymphoma over paediatric type follicular lymphoma.

The excision samples showed a “node in node” appearance with colonisation of germinal centres by small to medium-sized lymphoid cells, in 3 of the 4 excised lymph nodes; excision appeared complete.

Immunophenotype

This was essentially only fully assessable in the excision sample.

The B cells colonising germinal centres expressed BCL2, alongside weakly expressing IgD and MUM1, and subsets showed weak CD5 and CD43 positivity; they were negative for CD10 and BCL6.

Lambda light chain excess was evident in the colonising B cells and in the associated CD138+ plasma cells.

Germinal centres contained B cells showing a normal immunophenotype (CD10+, BCL6+, BCL2 (clone 124 & E17)-, appropriately elevated MIB1) and numerous PD-1+ T follicular helper cells.

Cytogenetics

FISH was performed on the FNA and core biopsy samples, and showed no evidence of BCL2 or BCL6 gene rearrangement, nor rearrangement at the DUSP22,IRF4 locus on 6p25.3.

Molecular Studies

B-cell clonality testing was performed on both the FNA and core biopsy samples. This showed clonal IGH and IGK gene rearrangements; a clonal IGL gene rearrangement was additionally detected in the core, but not the FNA sample.

Proposed Diagnosis

Paediatric nodal marginal zone lymphoma.

Interesting Feature(s)

The lymphoma showed marked follicular colonisation, which made interpretation of the FNA and core biopsy samples challenging. However, the use of molecular testing on the preceding samples led to faster final diagnosis on the excision so whilst unsuitable they were not uninformative.

EA4HP24-LYWS-8

Paediatric primary gastric MALT lymphoma with concomitant high-grade transformation, unusual presentation in adolescent.

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Case Description

A 13-year-old male patient been complaining of epigastric pain of one-year duration. One month prior to the presentation, he was diagnosed to have H. pylori associated gastritis. He received triple eradication therapy with no significant improvement. History of weight loss (4 kgs) was documented with no history of fever and night sweats. Upper GI endoscopy showed diffuse hyperemic gastric mucosa. CT scan showed focal wall thickening in gastric antrum and multiple enlarged left axillary lymph nodes largest measures 0.9 cm in its short axis. PET scan showed limited nodal disease in both axillary regions and limited bone metastasis in L2 vertebra and left iliac bone. Bone marrow biopsy was done and was negative for involvement by lymphoma.

Biopsy Fixation Details

The lymph node biopsy was fixed in 20% non-buffered formalin. Paraffin-embedded specimen was stained with routine Hematoxylin and Eosin (H&E) for histologic diagnosis.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Multiple gastric biopsies are examined, some are partially effaced by lymphocytic infiltrate composed of small mature looking lymphocytes admixed with few plasma cells and show occasional lymphoepithelial lesions. Ki67 among infiltrate shows low proliferative index (5%). Two additional biopsies show almost complete effacement of the architecture by

large lymphoma cells (centroblast/immunoblast) with high Ki67 proliferative index (80%). The lymphoma infiltrate is immunopositive for CD20, BCL2 and MUM1; and immunonegative for CD3, CD10, CD34, BCL6, TDT, and CD30. The background shows severe active H-pylori associated gastritis

Immunophenotype

CD20, BCL2, MUM1, CD3, CD10, CD34, BCL6, TDT, and CD30.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Paediatric primary gastric MALT lymphoma with concomitant high-grade transformation, unusual presentation in adolescent.

Interesting Feature(s)

Primary gastric lymphoma in children is uncommon and the majority are of high grade lymphoma. To our knowledge, this is the first case of concurrent low grade MALT lymphoma and high grade lymphoma (DLBCL) in a 13-year-old boy.

EA4HP24-LYWS-13

An unusual pediatric-type follicular lymphoma with marginal zone differentiation

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Case Description

•15 year-old boy who presented with a facial mass on left side

•Ultrasound showed a slightly complex hypoechoic lesion in preauricular soft tissue adjacent to the left parotid gland

HgB: 15.5 g/dL

HCT: 44.6%

WBC: 10.3 x 10^9/L

Platelets: 382 x 10^9/L

Differential Count (%; absolute value):

-Neutrophils: 71%; 7.3

-Lymphocytes: 20%; 2.1

-Monocytes: 7%; 0.7

-Eosinophils: 2%; 0.2

-Basophils: 0%; 0.0

Biopsy Fixation Details

- "Left parotid gland mass"
  - Weight: 4 grams
  - Dimensions: 3.0 x 2.4 x 1.5 cm
  - Ragged pink-red mass with fleshy and white cut surface
- Morphologic evaluation on a specimen fixed in formalin
- Flow cytometry was performed on a fresh fragment of tissue

Frozen Tissue Available

N/A

Details of Microscopic Findings

- Lymph node with effaced architecture
- Large expansile follicles with a serpiginous growth pattern:
  - Some with starry-sky pattern
  - Some expanded and some attenuated mantle zones
  - Composed of small mature lymphoid cells (predominant population) and large cells with the morphology of centroblast
- No geographic necrosis

Immunophenotype

Marker	Expression	Pattern
CD20	+	B cells mostly in expanded follicles
CD10	+	B cells in expanded follicles
BCL-6	+	B cells in expanded follicles
MUM-1	—	
BCL-2	—	
Cyclin D1	—	
SOX11	—	
CD43	—	
CD21	N/A	Expanded follicular dendritic cell (FDC) meshworks
CD23	N/A	Expanded FDC meshworks
IgD	N/A	Expanded mantle zones
Marker	Expression	Pattern
CD138	—	
Kappa & lambda IHC	—	
Kappa & lambda ISH	—	
CD30	—	

PD-1	N/A	Moderate-to-increased positive cells in follicles
Ki-67 proliferative index	N/A	High in expanded follicles Low in other areas

Cytogenetics

Negative FISH for the following rearrangements:

–Break-apart probes:

- *BCL2* (18q21.3)
- *BCL6* (3q27)
- *MYC* (8q24.21)
- *DUSP22*::*IRF4* (6p25.3)

–Dual fusion probe:

- *MYC* (8q24.2) :: *IGH* (14q32.3)

Molecular Studies

N/A

Proposed Diagnosis

Pediatric-type follicular lymphoma with marginal zone differentiation

Interesting Feature(s)

This case is unusual, sharing features of PTFL and PNMZL by WHO 2017

- PTFL features:
  - –Markedly expanded follicles
  - –Foci of attenuated mantle zones
  - –Germinal center B cells highlighted by CD10 and BCL-6
  - –Absence of BCL-2 expression
  - –Small CD10 positive kappa-restricted B cell population by flow cytometry
- PNMZL features including:
  - –IgD highlighting irregular and expanded mantle zones
  - –Variable PD1 positive cells in germinal centers, mostly increased to moderate number of PD1 positive cells
  - –Pushing PD1 positive cells to the periphery is not evident
- Therefore, we believe this case best classified as “pediatric-type follicular lymphoma with marginal zone differentiation” by ICC 2022 and PMID: 35609565

PTFL: Pediatric-type follicular lymphoma PNMZL: Pediatric nodal marginal zone lymphoma

EA4HP24-LYWS-31

Testicular follicular lymphoma in a 30-year-old man

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Case Description

30-year-old man with enlargement of the right testis for over a year. Serial ultrasound studies were suggestive of a granulomatous inflammatory condition. Right radical orchiectomy was performed. The testis measured 6.0 x 4.0 x 3.5 cm; on cross sectioning approximately 70% of parenchyma was replaced by a firm tan, fleshy appearing lesion. The lesion appeared to extend to the outer portion of the testis and also extended into peritesticular adipose tissue and epididymis. PET showed no evidence of lymphoma elsewhere (stage IE) and bone marrow was negative for involvement. The patient received 6 cycles of R-CHOP plus intrathecal methotrexate, as well as radiation to contralateral testis. He is alive with no evidence of disease, 7 years after initial diagnosis.

Biopsy Fixation Details

Formalin-fixed

Frozen Tissue Available

No

Details of Microscopic Findings

Testicular architecture is effaced by an atypical lymphoid infiltrate in a nodular pattern. Neoplastic nodules are composed of a mixture of predominantly larger centrocytes and variable number of centroblasts, overall meeting criteria for cytological grade 3A, follicular lymphoma. The neoplastic infiltrate shows focal destruction of the seminiferous tubules.

Immunophenotype

The lymphoma cells are positive for CD20, CD10 and BCL6, and are negative for BCL2.

Cytogenetics

FISH studies were negative for rearrangements of *BCL2, BCL6, IRF4* and 1p36.

Molecular Studies

Whole exome sequencing showed mutations in the following genes: *IRF8, BTG1, ALMS1, ARID1A, ETS1,* and *KLHL6.*

Proposed Diagnosis

Testicular follicular lymphoma (T-FL)

Interesting Feature(s)

This is a classic example of T-FL, a very rare neoplasm seen in children and young males (usually under 40 years of age). These cases usually show cytological grade 3A and are BCL2-negative. They have excellent prognosis and most do not require adjuvant therapy after orchiectomy. Limited data in the literature suggest that these cases overlap with pediatric FL. Our case showed *IRF8* mutation, a common genetic finding in pediatric FL.

Furthermore, our recent study on a series of T-FL showed that these lymphomas have frequent 1p36/*TNFRSF14* alterations (accepted for presentation at 2024 USCAP Annual Meeting, Baltimore, MD).

References:

1. Bacon CM, Ye H, Diss TC, et al. Primary follicular lymphoma of the testis and epididymis in adults. Am J Surg Pathol. 2007 Jul;31(7):1050-8.
2. Lovisa F, Binatti A, Coppe A, et al. A high definition picture of key genes and pathways mutated in pediatric follicular lymphoma. Haematologica. 2019 Sep;104(9):e406-e409.
3. Ozawa MG, Bhaduri A, Chisholm KM, et al. A study of the mutational landscape of pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma. Mod Pathol. 2016 Oct;29(10):1212-20.

EA4HP24-LYWS-34

A Case of Primary Testicular Follicular Lymphoma in a Young Adult Male

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Case Description

A 29-year-old healthy male presented in February 2023 in view of right testicular tenderness, without associated fever or hematuria. Clinical examination showed a firm testicular mass. Systemic examination was normal. Blood investigations were unremarkable. Urine PCR studies revealed *Chlamydia trachomatis*. Ultrasonography showed an 3.2cm area of geographic echogenicity in the lower pole of the right testis. A trial of antibiotics was initiated however, the mass persisted on serial imaging studies. Computed tomographic studies were normal. A right inguinal orchidectomy was performed.

Examination of the testicle showed a fleshy white tumour, measuring 43mm, involving the lower testicular pole, the hilum, the epididymis and the surrounding soft tissues, with focal adherhance of the tunica vaginalis. Histological analysis confirmed a neoplastic lymphoid infiltrate compatible with a primary testicular follicular lymphoma with areas of follicular (grade 3A) and diffuse growth.

Bone marrow studies were negative for involvement by disease. Four cycles of R-CHOP chemotherapy were administered with no adverse reactions. PET studies following chemotherapy showed complete disease remission. The patient remains well to date.

Biopsy Fixation Details

The testicle was preserved in 10% neutral-buffered formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

A lymphoid proliferation effaced the testicular parenchyma. Neoplastic lymphocytes extended between and infiltrated the seminiferous tubules, with associated sclerosis. The infiltrate was comprised of centroblasts and centrocytes, with the centroblastic infiltrate focally organised in discreet, non-polarised nodules with scattered intervening centrocytes, lacking tingible body macrophages. Areas of diffuse centroblastic infiltration were also evident. The infiltrate extended into the paratesticular soft tissues and epididymis, and infiltrated the tunica vaginalis. The background testicle was normal.

Immunophenotype

The centroblasts showed diffuse expression of CD20, confirming a B-cell phenotype. Expression of CD3 and CD5 was restricted to a background population of T-lymphocytes. The lymphoid blasts expressed BCL6 and, to a lesser extent, CD10 but were MUM1 negative. Weak, equivocal expression of BCL2 was noted in the blast population. Both CD30 and cyclin D1 were negative. A residual dendritic cell framework was highlighted on CD21 and CD23 stains in the areas of follicular growth, with framework effacement in areas of diffuse growth. The Ki67 proliferation index was around 80%. No expression of C-MYC was noted.

Cytogenetics

FISH analysis showed an IGH (14q32) rearrangement in 17% of cells. No rearrangements involving BCL6(3q27), MYC(8q24) and BCL2(18q21) were identified, confirming the absence of translocations between IGH and these loci.

Molecular Studies

N/A

Proposed Diagnosis

Primary testicular follicular lymphoma

Interesting Feature(s)

PTFL represents a rare lymphoma subtype with only around 20 cases reported. Most cases affect males younger than 16 years, with this case emphasizing the possibility of occurance of this lymphoma in the young adult population. Cases are typically t(14;18) *IGH:BCL2* negative. While PTFL represents a high grade follicular lymphoma subtype, cases typically present with Ann-Arbor Stage 1E disease and both extratesticular involvement and disese recurrence are virtually unheard of. Most patients are given adjuvant chemotherapy however, given disease rarity, universally accepted protocols are not in place for treatment and the utility of treatment has been questioned given the seemingly indolent nature of the disease.

EA4HP24-LYWS-36

Atypical B-cell proliferation with histological and immunophenotypic features of indolent paediatric B-cell lymphoma

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Case Description

This is a 9-year-old female with a two-month history of an enlarged posterior cervical lymph node, the size of which has not changed significantly. She had no significant clinical history and no other lymphadenopathy by imagine study.

Biopsy Fixation Details

The excisional lymph node was received in fresh and then fixed in 10% buffered formalin after a portion of the specimen was sent for ancillary studies.

Frozen Tissue Available

No

Details of Microscopic Findings

Sections revealed the lymph node architecture was effaced by nodular and vague nodular lymphoid proliferation. The majority of the cells are monotonous, small to medial in size, with slightly irregular nuclear contour, dispersed chromatin, inconspicuous or very small nuclei, and pale cytoplasm. Occasional apoptotic bodies and rare mitotic figures are seen. Few large activated lymphocytes with prominent nuclei are seen. Tangible body macrophages and mantle zones were near absent; no dark and light zones were present in the nodules.

Immunophenotype

Immunohistochemical studies showed CD21 highlighted the expansion of the germinal center dendritic mesh work in the effaced cortex and individual germinal centers. The majority of the cells in the effaced cortex and the nodules/germinal centers were positive for CD20, BCL-2, CD43 (weak), BCL-6 (subset/weak), and negative for CD10, CD30 and MUM-1. CD3 highlighted small amount of T-cells mainly between the nodules. Ki-67 labeling was approximately up to 30-40% in the B-cells. The immunostains of kappa and lambda light chains demonstrated the clusters or scattered polytypic plasma cells.

Flow cytometric analysis showed B-cell predominance without evidence of a light chain restricted B-cell population.

Cytogenetics

Not performed.

Molecular Studies

No evidence of clonal rearrangements of IGH or IGK immunoglobulin gene by RT-PCR.

Proposed Diagnosis

Lymph node, posterior cervical, excisional biopsy:- Atypical B-cell proliferation with histological and immunophenotypic features of indolent paediatric B-cell lymphoma

Interesting Feature(s)

1. A pediatric patient had an indolent clinical presentation with a single cervical enlarged lymph node.
2. Atypical lymphoid proliferation with some degree of histologic overlapping features between pediatric follicular lymphoma (PFL) and pediatric nodal marginal zone lymphoma (PMZL).
3. There was immunophenotypic ambiguity where the cells were positive for BCL6, favoring PFL, and they were negative for CD10 and positive for BCL2, unusual for PFL but favoring PMZL.
4. The histologic and immunophenotypic features were highly suggestive of an indolent pediatric B-cell lymphoma, i.e., PFL and PMZL.
5. However, there was no evidence of B-cell clonality as assessed by either flow cytometry, light chain immunohistochemistry, or IGH/IGK PCR.
6. The patient has been doing well after years of close clinical follow-up.

EA4HP24-LYWS-40

Pediatric-Type Follicular Lymphoma in a 15-year-old Male

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Case Description

A 15-year-old male presented with a four-month history of left cervical lymphadenopathy. Ultrasound examination revealed an enlarged lymph node measuring 2.3 cm at its largest dimension. Initial laboratory tests, including a complete blood count, basic metabolic panel, and lactate dehydrogenase, showed unremarkable results. Serological tests for EBV and CMV indicated past infections. Fine needle aspiration at an outside institution revealed abnormal lymphoid proliferation, raising suspicion for lymphoma and prompting a biopsy. Subsequent pathology assessment of the left posterior cervical lymph node excisional biopsy revealed pediatric-type follicular lymphoma (PTFL), negative for BCL2 gene rearrangement by fluorescence in situ hybridization (FISH). Staging computed tomography (CT) scans showed no signs of involvement by lymphoma at other sites. Bilateral bone marrow biopsies showed no morphologic or immunophenotypic evidence of lymphoma, normal male karyotype and negative FISH results for BCL2, BCL6, MYC, and IGH gene rearrangement.

The patient returned to the hospital within a month, reporting a non-tender, non-mobile palpable mass at the surgical site. A PET/CT scan revealed increased focal hypermetabolic

activity at the previous surgical site, with SUV max of 10.5, highly syspiccious of lymphoma. Another excisional biopsy confirmed PTFL. Due to disease clinical recurrence/ progression and proximity to vital structures, wide surgical resection was deemed inappropriate. Consequently, the patient underwent three cycles of R-CHOP chemotherapy. As of the last follow-up in 2019, there has been no clinical or radiologic evidence of lymphoma.

Biopsy Fixation Details

10% buffered formalin.

Frozen Tissue Available

NOT available.

Details of Microscopic Findings

Grossly, the specimen lacked a glistening surface and appeared partially removed. Histologic sections revealed lymphoid tissue with nodular proliferation of intermediate to large-sized atypical lymphoid cells admixed with small lymphocytes. The neoplastic lymphoid cells exhibited irregular nuclear contours, variably condensed chromatin, occasional nucleoli, and a moderate amount of cytoplasm.

Immunophenotype

Immunohistochemistry studies

The neoplastic cells exhibited positivity for CD20, CD10, and BCL6, but negativity for BCL2, and MUM1. EBV-ISH was negative. CD21 highlighted follicular dendritic cells meshworks. Ki67 proliferative index was approximately 50-60%. CD3 highlighted T cells.

Flow cytometry studies

Large population of monotypic B cells comprising 80% of the cells demonstrated:

- Positivity for CD19, CD20, CD38, CD10 (dim), and kappa light chain
- Negativity for CD5 and lambda light chain

Cytogenetics

Interphase FISH analysis performed on the lymph node involved by lymphoma (FFPE tissue) with breakapart probes targeting BCL2 was negative for BCL2 gene rearrangement.

Molecular Studies

Not performed

Proposed Diagnosis

Pediatric-type follicular lymphoma

Interesting Feature(s)

- This case reveals a rare diagnosis of pediatric-type follicular lymphoma that was clinically challenging.
- Unusual clinical course with a post-excisional biopsy imaging suggesting a new mass at the surgical site, raising concerns for residual/ recurrent disease. Upon correlation with clinicians' input and gross examination of specimens, it appeared that the entirety of the specimen had not been removed surgically due to anatomical complexity.
- While observation is the management of choice for pediatric-type follicular lymphoma, in this case, the concern for progression and the close proximity to vital structures prompted the decision for treatment with R-CHOP chemotherapy.

EA4HP24-LYWS-41

Enlarged cervical lymphnode in a young patient.

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Case Description
A 19 year old male patient presented with a single enlarged cervical lymphnode measuring approximately 3cm. Spleen was not enlarged.
An excisional biopsy of the lymph node was performed. The specimen was sent for consultation to exclude malignant lymphoma.
Biopsy Fixation Details
Formalin fixed, paraffin embedded.
Frozen Tissue Available
Frozen tissue not available
Details of Microscopic Findings
Enlarged, partially effaced lymphnode with preservation of the follicular architecture and a polymorphic interfollicular proliferation of monocytoid B-cells, small lymphocytes, plasmacytoid cells and blasts. Rare eosinophils. Sheets of blasts are not detectable. The B-cell follicles are large with irregular reactive germinal centres surrounded by a mantle zone. Marginal zones are not sharply demarcated.
Immunophenotype
The interfollicular lymphoid proliferation expresses CD20 and partially CD43 and is negative for CD10, BCL6, CD5, CD23, CyclinD1. Plasmacytoid cells show a light chain restriction (kappa). Ki67 is increased in the interfollicular compartment and high in the germinal centres. IgD highlights the mantle zones around the follicles. In a few but not in all follicles, the germinal centres are partially disrupted by the IgD-positive mantle cells. There are numerous PD1-positive cells in the BCL2-negative germinal centres.
Cytogenetics
Not done.
Molecular Studies
A B cell clone was detected by PCR fragment analysis (BioMed2-protocol)
and confirmed by NGS:
IgH FR1: clonal (IGHV3-30_18 and IGHJ4_02; 2,8%)
IgH FR2: clonal (IGHV3-30_18 and IGHJ4_02; 16,8%)
IgH FR3: not clonal
Ig-Kappa: clonal (IGKV3D-20_01 and IGKJ4_01; 5,2%)
Using a commercial NGS-Panel comprising 60 genes commonly mutated in lymphoid malignancies (ARID1A, ATM, B2M, BCL2, CDKN2A, DIS3, GNA13, ID3, MEF2B, SAMHD1, SOCS1, TNFAIP3, TP53, BCL6, BIRC3, BRAF, BTK, CARD11, CCND1, CCND3, CD79B, CREBBP, CXCR4, DNMT3A, EP300, ETV6, EZH2, FAM46C (TENT5C), FAS, FBXW7, FOXO1 (FOXO1A), HRAS, IDH2, IRF4, KMT2D/MLL2, KRAS, MAP2K1, MYC, MYD88, NFKBIE, NOTCH1, NOTCH2, NRAS,

PAX5, PIM1, PLCG2, POT1, PRDM1, PTEN, RHOA, RPS15, SF3B1, SGK1, SMARCA4, STAT3, STAT5B, STAT6, TET2, TNFRSF14 and XPO1) only a mutation of unknown clinical significance in the gene *MEF2B* (c.1046_1047delAG) could be detected.

Proposed Diagnosis

Pediatric nodal marginal zone lymphoma (PNMZL).

Interesting Feature(s)

Pediatric nodal marginal zone lymphoma with a predominant interfollicular growth pattern.

EA4HP24-LYWS-44

•Atypical proliferation of marginal zone with PTGC (due to polyclonal PCR result) vs pediatric marginal zone lymphoma

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Case Description

•10 year old girl wit unilateral enlargement of the tonsila of unknown duration
•She has normal immune status
•Thera are no enlarged lymph nodes anywhere else in the body
•The excision of both tonsils was performed

Biopsy Fixation Details

•Formalin fixed (10% buffered formalin) paraphine embeded

Frozen Tissue Available

No

Details of Microscopic Findings

•There is enlarged lonsil tissue with preserved nodularity.
•Ther surface epithelium is normal. There is a nodular proliferation of lymphoid tissue. Follicles are hyperplastic, there are some progressivly transformed germinal centers and abundant proliferation of small uniform lymphocytes occupiing the paracortex and inviding the follicles.

Immunophenotype

•CD20 +, bcl2 +, bcl6 -, CD10 -, CD5 -, CD23 -, CyclinD1 -.
•Proliferation marker MIB-1 labels cca.10-15% of the cells

Cytogenetics

Not performed

Molecular Studies

•PCR showed polyclonal B cell population

Proposed Diagnosis

•Atypical proliferation of marginal zone with PTGC (due to polyclonal PCR result) vs pediatric marginal zone lymphoma

Interesting Feature(s)

•The morphologic features favore pediatric MZL, but we could not proove the clonality of this lesion, so in that case we decided to coll this lesion atypical marginal zone hyperplasia with PTGC

EA4HP24-LYWS-63

Pediatric-type follicular lymphoma with extensive marginal zone differentiation

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Case Description

A 19-year-old male presented with a 6-9 month history of an isolated right neck mass. The mass was painless and he did not endorse any additional symptoms. An excisional biopsy was performed of the right level 2B lymph node.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections show portions of markedly enlarged lymph node with distorted architecture, characterized by variably-sized and enlarged and elongated distorted secondary lymphoid follicles. Germinal centers show distortion, elongation, and are characterized by intermediate-sized cells with high turnover and indistinct mantle zones. Prominent interfollicular areas show cells with more monocytoid features, including hyperchromatic nuclei and abundant pale cytoplasm. Diffuse sheets of large cells are not seen.

Immunophenotype

Follicle-based neoplastic B-cells express CD20 and PAX5, show expression of germinal center markers CD10, BCL6, and MEF2B, show an increased Ki-67 proliferation index (up to 90%), show lambda light chain restriction, and are negative for BCL2. In contrast, the interfollicular B-cell population shows less expression of germinal center markers CD10/BCL6/MEF2B, and and also shows lambda light chain restriction. Scattered lambda light chain restricted plasma cells are present throughout both areas. CD21 and CD23

highlight the expanded and distorted follicular denditritic cell meshworks underlying the distorted follicles.

Cytogenetics

FISH anaylsis showed no rearrangement of BCL2, BCL6, or IRF4.

Molecular Studies

A clonal immunoglobulin gene rearrangement was detected. NGS for B-cell lymphoma detected a *TNFRSF14* mutation c.169T>C, p.Cys57Arg, 19%, missense variant.

Proposed Diagnosis

Pediatric-type follicular lymphoma with extensive marginal zone differentiation

Interesting Feature(s)

While diagnostic features of pediatric-type follicular lymphoma (PTFL) are identified in a minority of the specimen; most of the specimen showed marginal zone differentiation, including plasmacytic differentiation, as seen in pediatric nodal marginal zone lymphoma (PNMZL). This case is an excellent example of PTFL showing a spectrum of disease that overalaps with that of PNMZL. Additionally, a TNFRSF14 mutation was detected, consistent with those reported in the literature.

EA4HP24-LYWS-64

Pediatric-type follicular lymphoma presenting as a nasopharyngeal polyp in a 30-year-old female

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Case Description

A 30-year-old female presented with nasal fullness and ear pain and was found to have a polypoid nasopharyngeal mass. The mass was excised and sent for pathologic evaluation. Following the diagnosis, the patient had PET/CT imaging that showed no other areas of disease, and a bone marrow biopsy was negative for involvement. The patient was considered to be Ann Arbor stage IE. The patient was treated with involved-site radiation therapy, without any systemic treatment. The patient remains free of disease 5 years from initial diagnosis.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The biopsy demonstrated polypoid respiratory mucosa containing a dense lymphoid infiltrate. In some areas, there were large and back-to-back abnormal follicles with irregular outlines and without surrounding mantle zones that contained a mixture of centroblasts

and centrocytes. In other areas, monocytoid cells were present, surrounding small lymphoid aggregates composed of small lymphocytes that were morphologically compatible with primary follicles.

Immunophenotype

The lymphocytes were CD20-positive B-cells, with coexpression of CD43. The abnormal-appearing follicles were positive for CD10, BCL6, MEF2B and HGAL, while the monocytoid areas exhibited expression of CD10 and weakly for HGAL, without significant BCL6 or MEF2B expression. BCL2 was negative to only weakly positive in the abnormal follicles, while it was positive in more monocytoid areas. IRF4/MUM1 was predominantly negative in the follicles but stained some cells at the periphery of the follicles. MYC stained only rare, scattered cells. Cyclin D1 and CD5 were negative on B cells. CD3 stained background T cells. CD21 stained expanded follicular dendritic networks. IgD demonstrated absence of mantle zones around the abnormal follicles and stained some primary follicles elsewhere. Kappa and lambda immunohistochemical stains highlighted rare polytypic plasma cells. Ki-67 was high in the abnormal follicles and low elsewhere.

Cytogenetics

Fluorescence in situ hybridization studies were negative for *BCL2*, *BCL6*, and *MALT1* rearrangements.

Molecular Studies

PCR was positive for monoclonal *IGH* rearrangement.

Sequencing studies identified a *MAP2K1* p.K57E mutation at a VAF of 35%.

Proposed Diagnosis

Pediatric-type follicular lymphoma

Interesting Feature(s)

This case has several unusual features. Pediatric-type follicular lymphoma is generally a nodal disease, but this case manifested as a nasopharyngeal mass. PTFL affects males far more commonly than it does females. The patient was 30 at presentation, emphasizing that PTFL may occur into young adulthood. The cells within the follicles did not exhibit a monomorphic centroblastic morphologic appearance as typically described for PTFL. Finally, although germinal center antigens were expressed widely in the tumor, this lymphoma had significant marginal zone differentiation, which, although well recognized in PTFL, raised diagnostic challenges. The identification of a *MAP2K1* mutation, along with the patient's young age and extensive germinal center antigen expression, aided in classification as a PTFL. The lymphoma has exhibited an indolent clinical course, with complete remission with only excision and localized radiation.

EA4HP24-LYWS-67

Pediatric-type follicular lymphoma with unusual features

Dr. Tapan M. Bhavsar

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Case Description

A 64-year-old male presented with a 2-cm right parotid tail mass, and a right superficial parotidectomy was performed.

Biopsy Fixation Details

Right superficial parotidectomy; fixed in 10% neutral buffer formalin

Frozen Tissue Available

Not applicable

Details of Microscopic Findings

Sections of the right superficial parotidectomy show variably-sized/shaped atypical nodular proliferation composed of small-to-medium sized lymphoid cells with variably clumped chromatin and occasional centroblasts (overall less than 5/high power field) with absence of polarization and tingible body macrophages – focally infiltrating in the adjacent adipose tissue. No cells with blastoid morphology are evident. Mantle zones are present – appear focally attenuated and show invagination/infiltration in few nodules, reminiscent of progressive transformation of germinal center-like changes. Mitotic activity appears low. No clusters/sheets of large cells.

Immunophenotype

The atypical lymphoid cells of the neoplastic follicles are positive for CD20, CD79a, BCL2, CD10 (moderate to strong) and BCL6; and are negative for CD5, CD23, CD43, MUM1 and cyclinD1. CD79a and IgD highlight the surrounding mantle zone cells with focal invagination in few nodules. Ki-67 highlights focal small collections/clusters of cells that are BCL2-negative and BCL6-positive, likely representing interspersed residual/reactive germinal center cells, and shows an overall low proliferative fraction (10-15%; 1+/4) in the atypical cell population. CD21 highlights expanded and focally fragmented follicular dendritic meshwork. CD3/CD5 and CD43 highlight few inter-follicular and occasional intra-follicular reactive T-cells; no atypia. CD138 stains few scattered inter-nodular polyclonal (kappa and lambda) plasma cells. CD30 stains occasional immunoblasts. p53, MUM1 and C-MYC (fewer) stain few variably-sized cells. CyclinD1 stains rare scattered histiocytes.

Cytogenetics

FISH analysis: Negative for t(14;18)IGH/BCL2 fusion; negative for BCL2, BCL6 and MYC gene rearrangements; and showed 3 intact BCL6 and BCL2 signals, suggestive of trisomy 3 and 18 respectively.

Molecular Studies

Molecular analysis for immunoglobulin gene receptor rearrangement performed showed positive IgH (FR 2: 267BP; FR 3: 100BP) and IgK (tube A: 135BP, 154BP, 279BP) gene rearrangements – confirming the presence of a clonal B-cell population.

Proposed Diagnosis

Pediatric-type follicular lymphoma

Interesting Feature(s)

(1) Strong BCL2 positivity (rather than conventional weak positivity/negativity); (2) Low grade cytology (rather than conventional intermediate high-grade blastoid morphology); (3) low proliferation index <30%; (4) absence of starry-sky pattern in the follicles; and (5) patient age > 40 yrs at presentation

EA4HP24-LYWS-70

A rare case of primary testicular follicular lymphoma in a pediatric patient

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Case Description

A 4-year-old male with no significant past medical history presented with scrotal swelling. He was found to have a 2.2 cm mass in the left testicle, and he subsequently underwent orchiectomy.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections of the left testicle revealed a dense lymphoid infiltrate forming small nodules/follicles between the seminiferous tubules. The infiltrate was composed of mostly intermediate-sized lymphocytes with round to irregular nuclear contours, vesicular chromatin, and small nucleoli admixed with occasional larger lymphoid cells. Mitotic activity was brisk.

Immunophenotype

The neoplastic cells were kappa light chain-restricted CD20/PAX5-positive B-cells that coexpressed CD10, BCL6, and MEF2B. They were associated with nodular CD21- and CD23-positive follicular dendritic cell meshworks. Ki-67 proliferation index was 80%. The neoplastic cells were negative for CD3, CD5, CD34, BCL2, cyclin D1, IgD, MUM1, MYC, and TdT.

Cytogenetics

No rearrangement of *BCL2* or *BCL6* and no deletion of the 1p36 chromosome (*TNFRSF14* gene) region was detected by interphase FISH.

Molecular Studies

Clonal immunoglobulin gene rearrangement was detected.

77-gene lymphoma NGS panel identified the following mutations:

Gene/allelic frequency:

GNA13/8.6%

RHOA/ 6.1%

TNFRSF14/ 26.4%

Chromosomal microarray:

Gain: 12p11.23-q24.33

Loss: 14q32.33-q32.33

LOH: 1p36.33-p36.32*

1p36.31-p36.22

1p32.2-p31.3

*LOH region with *TNFRSF14*

Proposed Diagnosis

Testicular follicular lymphoma

Interesting Feature(s)

Testicular follicular lymphoma (TFL) is an exceedingly rare diagnosis that is recognized as a distinct form of follicular lymphoma per the revised WHO 4th Edition Classification and International Consensus Classification. TFL shares some clinicopathologic features with pediatric-type follicular lymphoma (PTFL). TFL and PTFL both lack *BCL2* gene rearrangements and Bcl-2 protein expression, have a high mitotic rate, and may have *GNA13*, *RHOA*, and *TNFRSF14* mutations, as was demonstrated in this case. PTFL patients with a *TNFRSF14* mutation often have either concomitant 1p36 copy-number neutral loss of heterozygosity (common) or 1p36 deletion (rare). Deletion of 1p36 was absent but CN-LOH of the region with *TNFRSF14* was present in this case. Patients with TFL typically respond favorably to orchiectomy and chemotherapy and have excellent clinical outcomes.

EA4HP24-LYWS-95

An Unusual Case of an Enlarging Inguinal Mass in an Adult Man

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Case Description

A 41-year-old man with no significant past medical history presented with a left inguinal mass. He denied fevers, night sweats, or weight loss. Ultrasound revealed a 3 cm lymph

node that had been visible on imaging up to 7 years prior, when it measured 1.1 cm. An excisional biopsy was performed.

Biopsy Fixation Details

Fixed in formalin.

Frozen Tissue Available

None

Details of Microscopic Findings

H&E sections show an enlarged lymph node almost entirely replaced by a proliferation of enlarged and serpiginous follicles with expansile germinal centers composed of medium to large-sized cells with round to irregular nuclei, slightly dispersed chromatin, variably distinct nucleoli, and small to moderate amounts of cytoplasm. Numerous admixed tingible-body macrophages are seen within the follicles. The follicles lack polarization but show distinct mantle zones. No necrosis is seen. Focally, there is a rim of unremarkable secondary follicles at the periphery of the lymph node.

Immunophenotype

The follicles are composed of CD20+ PAX5+ B cells that co-express CD10, BCL6, FOXP1 (subset weak), IRF8, and are negative for CD5 and BCL2. CD21 and CD23 highlight intact follicular dendritic cell meshworks underlying follicles. Attenuated mantle zones are IgD+. PD-1 expression is not increased within follicles. The interfollicular space is composed predominantly of CD3+ T cells that co-express CD5 and BCL2. The Ki67 proliferation index is approximately 80% within follicles.

Cytogenetics

FISH studies did not detect a *DUSP22-IRF4* gene rearrangement, *TNFRSF14* (1p36) deletion, *BCL6* rearrangement, *MYC* rearrangement or *MYC* amplification, t(8;14), or *IgH/BCL2* t(14;18).

Molecular Studies

Next-generation sequencing revealed the following pathogenic variants: *MAP2K1* p.Q56P (VAF 15.1%) and *TNFRSF14* p.W12* (VAF 34.1%). No alterations were detected in the following genes: *BCL2*, *CREBBP*, *EZH2*, *KMT2D*.

Proposed Diagnosis

Pediatric-type follicular lymphoma.

Interesting Feature(s)

Pediatric-type follicular lymphoma (PTFL) is very rare in adults with a median age of presentation typically under 18 years. There are only several reported cases of patients over the age of 40, as in this case (PMID: 22855608, 35834399, 34877288). PTFL also typically involves the head and neck region; however, this case involved an inguinal lymph node. The biology of PTFL is not thought to be defined by age, as the mutational profile of *MAP2K1*, *TNFRSF14*, and *IRF8* are similar in pediatric and adult populations (PMID: 27325104). However, it has been understood more recently that these mutations are not exclusive to PTFL (PMID: 35609565, 35834399). Thus, further study is needed to understand the underlying biology as well as why PTFL is so rare in relatively older adults. In this case, both *MAP2K1* and *TNFRSF14* variants were detected, which occurs in only 20% of PTFL (PMID: 28533310). It has been proposed that *TNFRSF14* mutations precede *MAP2K1* in tumorigenesis based on higher allele frequency of *TNFRSF14* (PMID: 28533310), as in this

case. The *IRF8* p.K66R mutation is recurrent in a subset of cases (PMID: 27338637), but correlation with immunohistochemistry has yet to be established. In this case, *IRF8* mutation was not tested, but an immunostain showed intact expression. Another unusual feature of this case is the weak, subset positivity for FOXP1, which is typically strongly positive in PTFL (PMID: 31686194). Overall, this case involves unusual clinical features of a rare indolent pediatric lymphoma, as well as highlighting outstanding questions in the biology of this rare entity. At 6 months follow-up without additional treatment, the patient remains disease-free.

EA4HP24-LYWS-105

A Challenging Mimicker of Paediatric Nodal Marginal Zone Lymphoma

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Case Description

The patient is a 15 year old male with a history of mild hypotonia and developmental delay who presented with a 5 month history of painless, slowly enlarging right post-auricular lymphadenopathy. The patient denies fevers, night sweats, weight loss and bony pain.

Physical examination: 2.5 cm firm non-tender swelling behind the right ear with no overlying skin changes

Ultrasound: 2.4 cm complex cystic lesion with lobulated borders

Excision of the right cervical neck mass was performed.

Follow up PET/MRI scan showed right submental and level IIB hypermetabolic lymph nodes.

Three months later, a second cervical lymph node was excised.

Biopsy Fixation Details

Formalin-fixed

Frozen Tissue Available

N/A

Details of Microscopic Findings

Right postauricular mass excision

Lymph node with thickened capsule and architectural effacement by elongated and expanded follicles with perifollicular artifactual cracking. The pale interfollicular areas are expanded by small lymphocytes with monocytoid and plasmacytoid features.

Subsequent right level I cervical lymph node excision

Fragments of lymphoid tissue with vaguely nodal proliferation of small lymphocytes with monocytoid features. Focally, there are residual germinal centers which appear disrupted.

Immunophenotype

Right postauricular mass excision

IHC: Increased CD20+ B-cells within the interfollicular area that co-express BCL2, dim CD43 and MNDA (subset). CD10, BCL6, HGAL and MEF2B highlight diminished residual germinal center B-cells. CD21 and CD23 highlight the expanded disrupted FDC meshworks. IgD highlights extension of IgD positive B-cells into the germinal center. CD5, Cyclin D1, SOX11 and LEF1 are negative in the B-cell population.

Flow cytometry: Lambda-restricted B-cell population (5%) expressing dim CD10, CD19 and CD20, and negative for CD5 in a polyclonal background.

Subsequent right level I cervical lymph node excision

IHC demonstrated similar findings to right postauricular mass excision.

Flow cytometry: Kappa-restricted B-cell population (3.4%) expressing CD10, CD19, CD20, bright CD22, CD38, CD79b, CD200 and negative for CD5, in a background of polytypic B cells.

Cytogenetics

Not performed

Molecular Studies

Right postauricular mass excision

B-cell receptor (BCR) gene rearrangement studies by next-generation sequencing (NGS) detected IGK clonal immunoglobulin chain gene rearrangements (27.15%). No clonal immunoglobulin heavy chain (IGH) gene rearrangment detected.

Subsequent right level I cervical lymph node excision

BCR gene rearrangement studies by NGS detected IGK clonal immunoglobulin chain gene rearrangements (8.19%), with a dominant sequence that is different from the initial/diagnostic specimen. No clonal IGH gene rearrangment detected.

Proposed Diagnosis

Progressive transformation of germinal centers (PTGC). The presence of light chain restriction by flow cytometry and BCR NGS is most likely due to germinal centers.

Interesting Feature(s)

- Highlights a potential pitfall for practicing pathologists due to the remarkably similar morphologic and immunophenotypic findings seen in PTGC and PNMZL.
- Calls attention to the use of a monoclonal IgK and/or IgH gene rearrangement as distinguishing criteria in PNMZL. As seen in this case, PTGC may also demonstrate incidental clones on flow cytometry/BCR gene rearrangement NGS due to light-chain restricted germinal centers.
- At the time point of initial excision, diagnostic criteria for PNMZL was fulfilled. This case underscores the potential need for further refinement of the diagnostic criteria since the presence of a clonal IGK gene rearrangement may not be sufficient to distinguish between PTGC and PNMZL.

EA4HP24-LYWS-136

Pediatric type follicular lymphoma in a 39 year old female

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Case Description

A 39 year old female with no pertinent past medical history presented with a palpable enlarging right axillary lymph node but was otherwise asymptomatic. A right breast ultrasound showed multiple morphologically abnormal lymph nodes, BIRADS 4 and the initial core biopsy of the lymph node demonstrated an atypical B-cell proliferation. B-cell gene rearrangement studies detected a IgK kappa light chain gene rearrangement but a polyclonal IgH heavy chain gene. High-grade/Large B-cell lymphoma FISH panel was also normal. A subsequent excisional biopsy was performed for further evaluation.

Biopsy Fixation Details

The excisional biopsy was received in 10% neutral buffered formalin bottle before being grossly sectioned and subsequently embedded in paraffin. The paraffin blocks were sectioned at 3- to 4-mm in thickness and stained with hematoxylin-eosin or counterstained with hematoxylin for immunohistochemistry.

Frozen Tissue Available

No.

Details of Microscopic Findings

The excisional biopsy revealed an enlarged lymph node with expansile follicles exhibiting a serpiginous growth pattern but lacking polarization. The lymphoid follicles were composed of somewhat uniform medium to large centroblast-like cells with vesicular chromatin, occasional small nucleoli and moderate to abundant amount of eosinophilic cytoplasm. Scattered apoptotic bodies were also seen, as were some tingible body macrophages and mitotic figures. The mantle zones appeared attenuated and there was a background of fibrosclerosis with focal histiocyte aggregates.

Immunophenotype

The neoplastic follicles were composed of CD20 positive B-cells that were also positive for BCL-6, and FOXP1, but negative for BCL-2 and MUM1. The Ki-67 nuclear proliferation index within these follicles was about 80-90%. HHV8 staining was also negative.

Cytogenetics

High-grade/large B-cell lymphoma FISH panel testing for BCL6 rearrangement, MYC rearrangement, MYC amplification, and BCL2 rearrangement were performed but no rearrangements or amplifications were detected. FISH studies were also negative for DUSP22-IRF4 rearrangement.

Molecular Studies

BCL2 translocation by PCR was not detected but B-cell gene rearrangement by PCR was detected.

Proposed Diagnosis
Pediatric type follicular lymphoma (PTFL)
Interesting Feature(s)
This case is very interesting due to the atypical clinical presentation combined with the more classic morphologic and immunohistochemical findings. The majority of cases of PTFL occur in those less than 25 years old with a male predominance of 10:1 making our case of a 39 year old female an unlikely presentation. Additionally, a recently described marker, FOXP1, was positive in our case, and was previously found to be almost uniformly positive in PTFL cases compared to reactive germinal centers in follicular hyperplasia. FOXP1 belongs to a transcription factor family and has been shown to be involved in B cell development, immune regulation and reportedly represses plasma cell differentiation.

EA4HP24-LYWS-150

Ileocecal Mass in a 3yo Male

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Case Description
The patient is a 3-year-old male who presented to the Pediatric Emergency Department with abdominal pain concerning for ileocecal intussusception. As the intussusception was not reducable, he underwent exploratory laparotomy and a 3.2cm portion of ileum attached to a 4.8cm section of cecum was excised. The appendix (3.7cm x 2.1 cm) had a 4.9cm submucosal mass extending into the cecum.
Of note, the patient had a past medical history notable for failure to thrive and sleep apnea requiring bilateral tonsillectomy at an outside hospital. The tonsils were not examined microscopically but were reportedly markedly enlarged for age (report not available).
Biopsy Fixation Details
Ileocecal segment was fixed in neutral-buffered formalin after a portion of the mass was sent for flow cytometry.
Frozen Tissue Available
None
Details of Microscopic Findings
Sections show intestinal mucosa with a dense lymphoid infiltrate with follicular lymphoid hyperplasia. The follicles show germinal center polarity, contain tingible-body macrophages, centrocytes and centroblasts. The reactive follicles have a thin and attenuated mantle cuff with expanded marginal zones. The marginal zones contain small to medium-sized cells, some with monocytoid features, as well as larger immunoblastic forms and plasmacytoid forms. Deeper in the submucosa, the follicles become more

attenuated with larger nodules of small to medium-sized lymphocytes colonizing follicles and spanning the interfollicular space.

Immunophenotype

The reactive follicles are clearly defined by CD21+ follicular dendritic cell meshworks with germinal center B cells expressing appropriate CD20, PAX-5, CD10, BCL-6 and negative for BCL-2. The follicles are surrounded by small, CD3+ CD5+ T cells as well as a more prominent expanded marginal zone. These marginal zone B cells express CD20, PAX-5, BCL-2 and are negative for CD5, CD10, BCL-6, Cyclin D1, and c-Myc. CD30 highlights perifollicular immunoblasts. The Ki-67 proliferative rate is 70-80% in the marginal zone B cells. EBV encoded RNA by in situ hybridization (EBER) is negative in the lymphocytes. Further immunohistochemistry for pERK, IgD, Kappa and Lambda performed at the NIH confirmed the histologic impression of follicular lymphoid hyperplasia and marginal zone hyperplasia with some evidence of lambda light chain restriction, partially within the follicle centers.

By flow cytometry, B cells were increased (69% of total cells), a subset of which (34% of total cells) had the following abnormal immunophenotype: lambda-restricted (negative for kappa); positive for CD10, CD19, CD20, CD38 (heterogeneous); and CD45 (bright); negative for CD5, CD23, CD34, and CD200; and variably increased forward scatter. The remaining B cells are polytypic with a normal immunophenotype. T cells were a mix of CD4 and CD8 subtypes with normal expression of CD5 and negative CD10. There was no significant increase in double-negative T cells (CD3+CD4-CD8-).

Cytogenetics

None

Molecular Studies

Polyclonal for Ig rearrangements

Proposed Diagnosis

Atypical Marginal Zone Hyperplasia

Interesting Feature(s)

As a reactive expansion of B cells, atypical marginal zone hyperplasia can be mistaken for a B cell lymphoma such as marginal zone lymphoma or follicular lymphoma. The finding of a monotypic lambda-restricted population of polyclonal B cells has been reported previously in this entity. Key features to distinguish this diagnosis from malignancy include localized presentation to native MALT sites, polyclonality on immunoglobulin PCR and naive-B cell immunophenotype without chromosomal or molecular alterations characteristic of lymphoma.

EA4HP24-LYWS-187

Pediatric-Type Follicular Lymphoma Presenting as a Conjunctival Mass.

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Columbia University Irving Medical Center, Department of Pathology and Cell Biology, New York, USA

Case Description

A 14-year-old female presented with a 2-month history of conjunctival mass. PET-CT showed no evidence of systemic disease. The mass was entirely resected. The patient received no therapy and is currently disease-free (4 months of follow up).

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

Sections show multiple small fragments of conjunctiva with an atypical subepithelial lymphoid infiltrate. Focally, the infiltrate demonstrates enlarged irregular follicles with ill-defined mantle zones. The germinal centers are comprised of intermediate- to large-sized cells with blastoid appearance. A portion of the biopsy shows residual reactive lymphoid tissue.

Immunophenotype

Immunohistochemistry: CD20+, CD79a+, CD10(strong)+, BCL6+, BCL2-, MUM1-, FOXP1+, CD5-, CD30-, CD43-, CyclinD1-, c-MYC-, and P53-. The Ki-67 proliferation index is elevated in the blastoid cells. Expanded irregular follicular dendritic cell meshworks are highlighted with CD21 and CD23 stains.

Flow cytometry: CD19(bright)+, CD20+, CD79a+, CD22(dim)+, CD10(bright)+, CD23-, CD38(bright)+, CD200-, CD5-, CD30-, CD43-, CD103-, and kappa+.

Cytogenetics

FISH: LSI 1p36/1q25 and IRF4-DUSP22 probes showed no evidence of deletion or rearrangement.

Molecular Studies

Immunoglobulin heavy chain (*IGH*) multiplex polymerase chain reaction (PCR) showed a clonal gene rearrangement using primers for frameworks 1, 2, and 3.

NGS studies did not identify any pathogenic mutations.

Proposed Diagnosis

WHO: Clonal proliferation with features of pediatric-type follicular lymphoma.

ICC: Pediatric-type follicular lymphoma.

Interesting Feature(s)

Ocular adnexal lymphoma (OAL) is exceedingly rare in the pediatric population, and when observed, generally represents an extranodal marginal zone lymphoma or diffuse large B-cell lymphoma. The current case shows a clonal proliferation with features of pediatric-type follicular lymphoma (PTFL), which has rarely been reported in the ocular adnexal region.
PTLF is an indolent B-cell lymphoma typically presenting as localized disease in head and neck lymph nodes of pediatric patients. Histologically, PTFL is characterized by enlarged follicles containing expansile germinal centers comprised of medium to large blastoid cells. The neoplastic cells express CD10, BCL6, and show aberrant FOXP1 expression, but do not express BCL2 or MUM1. Clonality can be demonstrated by flow cytometry and/or *IGH* PCR. *BCL2*, *BCL6*, and *IRF4* rearrangements are not present. Structural alterations involving chromosome 1p36 (25-40% of PTFL) and mutations of *TNFRSF14* (44-54%), *MAP2K1* (43-49%), and *IRF8* (15%) may be seen.
This case, and many of the previous 10 cases of OAL PTFL-like proliferations reported in the literature, showed clinicopathologic features that are nearly identical to PTFL at nodal locations, acknowledging that certain architectural features are not evaluable in small conjunctival biopsies. Whether conjunctival PTFL-like lesions should be classified as PTFL can be debated - according to the current 2022 WHO guidelines, extranodal PTFL-like proliferations are not classified as PTFL, while the currently available 2022 ICC guidelines do not explicitly stipulate localization in PTFL diagnosis. Given the rarity of conjunctival PTFL-like proliferations, it is not clear if they share overlapping molecular alterations typical of PTFL. The only previously sequenced conjunctival PTFL-like lesion harbored a *MAP2K1* mutation, however, our study did not identify any pathogenic mutations, including in *MAP2K1*, *TNFRSF14*, or *IRF8*.

EA4HP24-LYWS-209

Pediatric nodal marginal zone lymphoma

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Case Description

- 29/M presenting with enlarged left cervical lymph node since 19 years old, progressively increasing in size.
- Developed new enlarged lymph node (submental)
- No B symptoms, otherwise well
- Physical examination: Submental, left cervical and left occipital LN
- Left cervical and occipital LN excised
- CT scan: No other lymphadenopathy or extranodal involvement
- BM biopsy: negative

- Patient relapsed 1.5 years later with enlarged left cervical lymph node. Biopsy showed pediatric NMZL with increased large cells
  - PET scan: No definite hypermetabolic lymphadenopathy or extranodal pathology
  - BM biopsy: Negative
  - Post nasal space biopsy: Atypical B cell infiltrate
- Patient treated with radiation therapy (RT)
- Post RT CT scan showed disease resolution
- Patient well 6 months post RT

Biopsy Fixation Details

Specimen was fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Nil

Details of Microscopic Findings

• Large hyperplastic follicles with progressively transformed germinal centres (PTGC)-like changes

• follicles show prominent and hyperplastic mantle zones cells expanding and disrupting the germinal centres

• The marginal zone and interfollicular region show an atypical lymphoid infiltrate composed mainly of small to medium-sized lymphocytes and scattered large lymphocytes with vesicular nuclei with irregular nuclear membranes and contain one or more nucleoli. Some lymphocytes contain a rim of pale to clear cytoplasm, resembling monocytoid cells

• The lymphoid infiltrate disrupt/colonize some follicles

• There is no prominent plasmacytic differentiation.

Immunophenotype

• CD20 and CD79a highlight increased numbers of B cells in the interfollicular and paracortical region.

• The interfollicular B cells do not coexpress CD10, CD5, CD23 or cyclin D1.

• Suggestion of weak CD43 co-expression in some of the interfollicular B cells (Pax5/CD43 double stain performed).

• The germinal centres are reactive (CD10/BCL6+/BCL2-)

• IgD highlights the prominent mantle zones and PTGC-like appearance.

• CD21 and CD23 stains for the follicular dendritic meshwork, which show patchy disruption in focal areas.

• Ki67 proliferation index is about 40% in the interfollicular region.

• CD3 and CD5 highlights reactive T cells predominantly in the interfollicular regions and they do not show significant nuclear atypia.

• No light chain restriction

• EBER negative

Cytogenetics

Normal: 46,XY

Molecular Studies

IgH/IgK PCR monoclonal

Proposed Diagnosis

Pediatric nodal marginal zone lymphoma

Interesting Feature(s)

- This is a case of pediatric nodal marginal zone lymphoma (PNMZL) with typical clinical presentation and morphologic features
  - clinical presentation (young, male localized disease in head and neck lacks B symptoms)
  - morphologic features: interfollicular expansion of marginal zone cells, PTGC-like features, follicular colonization
- Prognosis
  - most patients with limited stage PNMZL underwent watchful waiting after complete resection
  - < 5% relapse (as illustrated in this case), often cured with second-line therapy.

EA4HP24-LYWS-254

Plasma Cell Proliferation With Atypical Features in a Pediatric Patient

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Case Description

Renal mass detected in the CT scan of a 17-year-old male patient with Hepatitis B. The mass was located in the lower pole of the left kidney, with a diameter of 4 cm and no clear capsule. Differential radiological diagnosis included renal medullary tumors or renal cell carcinoma. A core needle biopsy showed a dıffuse ınfiltrate of mature plasma and plasmacytoid cells without dysplasia. CD138 and IgG were diffusely posıtıve and CD117 partially positive. The kappa-lambda ratio was nearly identical (1:1). CD20, CD56, cyclinD1,IgM, IgA, IgD and IgG4 were negative. Ki-67 was 5%. In bone marrow aspiration, the plasma cell ratio was 5% without abnormal phenotype. Electrophoresis of perıpheral blood showed polyclonal hypergammaglobulinemia without a monoclonal band. No proteinuria was detected. IgG levels were increased (17,6 g/L). For further examination and definitive diagnosis, excision of the mass with partial nephrectomy was performed. The patient received no further treatment and has been followed for 6 months without progression or relapse.

Biopsy Fixation Details

Formalin-fixed and paraffin-embedded tissue

Frozen Tissue Available

Not Available

Details of Microscopic Findings

Lesion in kidney parenchyma consists of mature plasma and plasmacytoid cells. Some cells are atypical, with large prominent nucleoli and loose chromatin. Intracytoplasmic eosinophilic vacuoles are observed ın some cells. Occcasıonal eosınophıls, lymphoid cell aggregates and occasionally follicles with germinal centres are observed. The stroma has bands of collagen intermingled between the cells with some hyalinized areas. Dystrophic calcifications are present.

Immunophenotype

Cells are dıffusely positive for CD45, CD79a and MUM1 and partıally for CD138, CD19 and CD117. Kappa and Lambda ratio is around 1:1. CD20, CD56, CyclinD1, CD10, IgG4, PAX8 and CAM 5.2 are negative. EMA is variably positive. IgG is dominantly positive in the study of heavy chains; fewer cells were positive with IgA, IgD and IgM. CD3 stained T cells. EBER and HHV8 are negative. Ki-67 is around 5%.

Cytogenetics

FISH studies were performed ifor myeloma panel. No alterations were detected for IGH(14q32) and CDKN2C/CKS1B; TP53 was not evaluable.

Molecular Studies

Clonality studies for IgH (FR1, FR2 and FR3) showed polyclonal rearrangements. NGS study with lymphoma panel was performed in the tru-cut biopsy, and no mutation was detected.

Proposed Diagnosis

Plasma Cell Proliferation With Atypical Features

Interesting Feature(s)

This case presents an atypical plasma cell proliferation with abnormal immunophenotype. While clonality, NGS, and FISH studies did not support any clonal process, the possibility of neoplastıc proliferation with massive plasmacytic differentiation cannot be ruled out due to abnormal phenotype with CD117 positivity, CD19 loss, and IgG-dominant monotonous staining. Although the relationship between MZL and hepatitis C is known, our patient had a hepatitis B infection, which does not fit the clinical picture for MZL. Plasmacytoma/plasma cell dyscrasias are not typically expected in this age group, but reports of cutaneous and systemic plasmacytosis with polyclonal hypergammaglobulinemia characterized by skin lesions are reported in the literature. However, presentation with only a peripheral mass in the kidney is rare. In conclusion, this is an interesting case that rises the differential diagnosis of reactive vs neoplastic plasma cell proliferation. The lack of clonality and NGS alterations, along with indolent course would favor reactive but the cells have an abnormal phenotype.

EA4HP24-LYWS-269

An asymptomatic healthy 8-year-old boy presenting with intramuscular fluctuating mass

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Case Description

A healthy 8-year-old boy with intramuscular mass of the deltoid muscle with satellite adenopathies that appeared in 2021, with fluctuating evolution. Complete surgical resection in 2021: reactive lymphoid proliferation. Reappearance of an isolated 40 mm deltoid mass with homolateral axillary adenopathy (reactive lymph node on histopathological analysis), on PET scan

Biopsy Fixation Details

2 centimetric needle biopsy fragments in formol

Frozen Tissue Available

Yes

Details of Microscopic Findings

Dense & diffuse lymphoid infiltrate in striated skeletal muscle with scattered follicles with germinal centers and no recognisable LN structure. Follicles are of varying size with non-homogenised GC, surrounded by a preserved mantle zone. Marked expansion of interfollicular areas, somewhat pale-appearing and polymorphous, including small lymphocytes (sometimes clarified with a monocytoid like appearance), lymphoplasmacytic and non-atypical plasma cells, associated with numerous histiocytes sometimes grouped in epithelioid clusters, without necrosis. Rare neutrophil contingent. No large atypical Reed Sternberg or Hodgkin cells. Moderate vascular hyperplasia.

Immunophenotype

CD20 is expressed in lymphoid follicles but also heterogeneously by small lymphocytes in the interfollicular zones mixed with numerous mature CD5+ T lymphocytes and numerous CD138+ plasma cells. The plasma cell population is monotypic Kappa and expresses IgG 4. Two intensities of CD138 labelling in the interfollicular zones should be noted: high in the plasma cell population and low in the lymphoplasmacytic population identified by flow cytometry. Focal colonisation of germinal center by the IgG kappa plasma cell differentiated population. Positivity of mantle cells with Ig D with some moderately hypertrophic zone and negativity of the majority of the interfollicular lymphoid population. EBER and HHV8-. Ki67 (20 - 30%)

30% of lymphocytes are B CD20+ with 2 distinct monotypic kappa subpopulations; one is lymphoplasmacytic: CD19+/CD20-/CD38+/CD138-/ kappa+ and the other lymphocytic CD19+/CD20+ strong/ kappa +

Cytogenetics

Not done

Molecular Studies

No detectable mutation .Monoclonal B population

Proposed Diagnosis

Intramuscular localisation of a MALT lymphoma with IgG4 kappa plasmacytic differentiation "of primary cutaneous type" according to WHO 2022

Primary cutaneous lymphoproliferation of the marginal zone according to the ICC, IgG isotype IgG4

Interesting Feature(s)

Unusual localisation of an uncommon B cell lymphoma arising in a child (less than 10 year-old), with plasmacytic differentiation showing IgG4 expression. It has been shown in marginal zone lymphoma involving the skin, that expression of IgG4 was invarriably be of primary cutaneous origin with an extremly low risk of spread to noncutaneous sites and having an excelent prognosis

Beside a vaccination 2 years before the first lesion appeared in 2021, no other etiological factors have been found, such as chronic infection (Borrelia Burgdoferi) or chronic inflammatory stimuli (tatoo, radiation therapy)

References

- Xu Z, et al. A healthy 16-year-old boy presenting with multifocal asymptomatic subcutaneous nodules.Pediatr Dermatol. 2022 Jan;39(1)
- Brenner I, et al. Primary cutaneous marginal zone lymphomas with plasmacytic differentiation show frequent IgG4 expression. Mod Pathol. 2013 Dec;26(12):1568-76
- Carlsen ED, et al. Class-switched Primary Cutaneous Marginal Zone Lymphomas Are Frequently IgG4-positive and Have Features Distinct From IgM-positive Cases. Am J Surg Pathol. 2019 Oct;43(10):1403-1412.
- Swerdlow SH. Cutaneous marginal zone lymphomas. Semin Diagn Pathol. 2017 Jan;34(1):76-84

EA4HP24-LYWS-304

A lesion of the labia minora in a 13-year old girl

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Case Description

A 13-year old girl presented with a protruding, tender mass in the labia minora (ventral side), sonografically 2,6 cm in diameter, which appeared two weeks before the first presentation

in the Gynecology department. The mass was incompletely excided after one week from the first physical examination and completely excided after about two months. A bone marrow biopsy was negative. The blood tests showed a light anemia but no other significant alterations. Lymphadenopathy or splenomegaly was not reported. The patient was lost to follow-up after 3 months following the complete resection. The presented material comes from the first resection.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The biopsy shows a superficial squamous epithelium (labia minora) and an extensive dermal infiltration by a mostly follicular appearing lymphoid infiltrate. The follicles show variable size, focally reduced/absent mantles and focal confluency of atypical germinal centers, which lack tingible-body macrophages and consist of a mixed population of large centrocytes and centroblasts (> 15/HPF), mitoses are frequently encountered. Intermixed between the atypical follicles some small lymphocytes.

Immunophenotype

The atypical cells are positive for CD20, CD10, BCL6 and partly for CD23. BCL2 is expressed predominantly in the T-cells, however some larger B-cells show a weak staining. Atypical cells are negative for CD5, although numerous intermixed T-cells cause some interpretation difficulties. EBER is negative. Proliferation index (Ki-67) is about 40-50%.

Cytogenetics

N/A

Molecular Studies

B-cell clone detected in the sending institution. 43-gene NGS-Panel (ATM, B2M, BCL2, BIRC3, BRAF, BTK, CARD11, CCND3, CD79A, CD79B, CREBBP, CXCR4, EP300, EZH2, FOXO1, H1-4, ID3, IRF8, KLF2, KMT2C, KMT2D, MAP2K1, MEF2B, MYC, MYD88, NFKBIE, NOTCH1, NOTCH2, NSD2, PIM1, PLCG2, PTPRD, RRAGC, SF3B1, SGK1, SOCS1, STAT6, TBL1XR1, TCF3, TNFAIP3, TNFRSF14, TP53, XPO1) showed no alterations.

Proposed Diagnosis

Follicle center cell lymphoma of the lower genital tract in a pediatric setting (after exclusion of systemic follicular lymphoma).

Interesting Feature(s)

Follicle center cell lymphoma of the lower genital tract (Saksena A et al. Am J Surg Pathol. 2023 Mar 1;47(3):409-419. PMID: 36461146) is considered a variant of primary cutaneous follicle center cell lymphoma arising in the lower genital tract, which normally affects women in the 4^{th}-5^{th} decade. To our knowledge, this is the first case reported in a pediatric setting. Also primary cutaneous follicle center cell lymphomas are particularly rare in the pediatric population, with less than 15 reported cases in the literature. We could detect no mutations in our case, however some of the recurrently mutated genes reported by Saksena et al. are not present in our small panel (most notably *XIAP*).

EA4HP24-LYWS-314

Atypical Marginal Zone Hyperplasia in an Adolescent

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Case Description

A 14-year-old male presented to an outside facility in May 2023 with sore throat and enlarged left tonsil. He was treated with antibiotics, without resolution. CT scan revealed a left tonsillar mass and an enlarged cervical node. He underwent tonsillectomy in 11/2023. Flow cytometry and molecular studies [PCR for *IGH* gene rearrangement and FISH for *IGH::BCL2* (dual fusion) and *IGH* (break apart probe)] were negative. Due to concern for a lymphoma, the patient was referred for evaluation. Imaging at our institution (11/2023) revealed an enlarged left level II cervical lymph node (2.8 x 1.8 cm). No additional lymphadenopaty in the neck, chest or abdomen was identified. An excisional lymph node biopsy was performed.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Sections of the tonsil show enlargement with marked follicular hyperplasia. The follicles are enlarged, vary in size and show expansion of the marginal zones; in addition, disrupted germinal centers are also noted with progressive transformation of germinal centers (PTGC) like changes. The interfollicular areas consist of small monocytoid cells. In areas, the mantles are attenuated. Examination of the subsequent lymph node (LN) biopsy showed similar findings.

Immunophenotype

Immunostains in the tonsil for CD20/PAX5 highlights reactive follicles and interfollicular monocytoid B-cells. A subset of these B-cells appear to weakly express BCL2, and they are negative for CD5, CD43, CD30, CD15, MUM1, CD10, BCL6, CD43, cyclin D1, and MYC. CD10 and BCL6 demonstrate residual reactive and partially disrupted germinal centers compatible with PTGC changes. CD21/CD23 highlights expanded follicular dendritic meshworks. The proliferation index is overall low (10-20%), and restricted to residual germinal centers mainly, as demonstrated by Ki-67. PD1 demonstrates small follicular T-cells. OCT2/BOB1 show follicular B-cells, without any atypical large population present. In-situ hybridization for EBV-encoded RNA (EBER) is negative. There are lambda light chain restricted cells within the follicles, demonstrated by kappa and lambda stains (both in situ hybridization[tonsil] and IHC [LN]). The few plasma cells present are polytypic.

Flow cytometry on the lymph node did not identify any monoclonal B-cell or aberrant T-cell populations; however, the kappa to lambda ratio of the mature B-cells was slightly lambda skewed (kappa to lambda ratio = 0.8:1).

Cytogenetics

Not performed

Molecular Studies

PCR studies, on both the tonsil and lymph node samples, for *IGH* gene rearrangement (Biomed 2, Tubes A-E) showed a polyclonal pattern.

FISH on the lymph node was negative for translocation *IGH::BCL2* (dual fusion) and negative for rearrangement of *IGH* (break apart probe).

Proposed Diagnosis

Atypical Marginal Zone Hyperplasia

Interesting Feature(s)

The morphologic, immunophenotypic and molecular features favor a benign lymphoproliferation on both the tonsil and cervical lymph node. We favor this to be an atypical marginal zone hyperplasia with focal progressive transformation of germinal centers. Such cases have rarely been described in tonsils of children and demonstrate monotypic, but polyclonal, marginal zone cells. Interestingly, these cases have only been reported so far only in tonsils and appendix. Involvement of lymph nodes has not been reported. Thus, the spectrum may be extended to lymph nodes. Another interesting feature is the identification of lambda light chain predominant intra-follicular B-cells (better appreciated by immunohistochemistry than in-situ hybridization).

EA4HP24-LYWS-345

Isolated lymphadenopathy in a young adult

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Case Description

A 23-year-old male presented with a three month history of swelling in the right neck. Examination revealed an enlarged right level I cervical lymph node. Excisional biopsy was recommended and undertaken (submitted case). Staging studies revealed no disease elsewhere (stage 1A).

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Much of the node is filled with very large, closely packed follicles containing irregular follicle centres filled by a relatively monotonous population of intermediate size lymphoid cells with scanty cytoplasm, variably dispersed nuclear chromatin and multiple nucleoli. There are scattered mitotic figures and relatively frequent apoptotic bodies but no zonation pattern. Mantles are variably well formed and many of the follicles are in part surrounded by an expanded marginal zone populated by intermediate size lymphoid cells with more abundant pale staining cytoplasm. In addition, around the periphery of the node, there is a rim of normal appearing lymphoid tissue in which reactive follicles with more typical appearing germinal centres are seen.

Immunophenotype

Cells in the large atypical follicles have the following phenotype:

- Positive: CD10, CD20, BCL6.
- Negative: CD3, CD5, CD23, BCL2, IRF4, cyclin D1.
- Ki67: >95%

Cytogenetics

ND

Molecular Studies

IdentiClone PCR assays (InvivoSCribe Technologies) revealed clonal IG gene rerrangement (IGH tube A, IGH tube B, IGK tube A).

Next Generation Sequencing: Material sequenced using HMDS Pan-HaemOnc Assay with analysis limited to virtual panel of lymphoid genes (see PPT presentation). No reportable variants detected.

Proposed Diagnosis

Paediatric-type follicular lymphoma.

Interesting Feature(s)

Paediatric-type follicular lymphoma (PT-FL) was recognized as a distinct entity in the 2017 WHO classification. Originally described in children, it may also be encountered in young adults (median age 15-18 years) and is rare in adults over the age of 40. Most cases present with isolated lymph node enlargement and prognosis is excellent. By definition, cases lack rearrangements of *BCL2, BCL6, MYC* and I*RF4.* Diagnosis is often challenging as the phenotype of the neoplastic cells mirrors that seen in reactive germinal centres; CD10+, BCL6+, BCL2-, IRF4-. Demonstration of clonality (as in this case) can help make the diagnosis but should always be interpreted with caution since clonal IG gene rearrangements may occasionally be encountered in reactive lymphoproliferations. Next generation sequencing is therefore a useful adjunct to diagnosis as it can confirm a clonal genetic abnormality. The genomic profile is different from that of conventional follicular lymphoma, with a high frequency of *MAP2K1* mutations, *1p36/TNFRS14* alterations (30–70%) and mutations of *IRF8* (15–50%). Conversely, and in contrast to FL, mutations in epigenetic modifiers are uncommon (*KMT2D, CREBBP, EP300, MEF2B, EZH2*).

Our case showed evidence of marginal zone differentiation. This is frequently seen in PT-FL and there is an emerging consensus that pediatric-type nodal marginal zone lymphoma is part of the spectrum of PTFL, both disorders sharing similar molecular profiles, clinical presentations, and outcomes.

Whilst we failed to find *MAP2K1* or any other mutations in our case, we felt that the clonal

nature of the process and pathological features justified a label of PT-FL. Given the localized nature of teh disease and excellent outcome associated with this diagnosis, a watch and wait policy was initiated following surgical excision. The patient was alive and disease free when last seen, 6 months after diagnosis.

EA4HP24-LYWS-348

Florid nodular lymphoid hyperplasia of the appendix

Dr. Laura Bandiera

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Case Description

A 12 year old boy presented in emergency room with abdominal pain and mild fever; nausea and vomiting for 2 days.
Tender abdomen with Blumberg+.
WBC 6900/mmc (N 62%, L 19%), Hb 14.1 g/dL, PLT 342000/mm3, C-RP 1,2 mg/dL.
Ultrasonography showed a slight thickening of the appendix (8-9 mm diameter), no periappendiceal fluid, no lymphadenopathies (max 7 mm).
An appendectomy was performed in the suspicion of acute appendicitis; the appendix was routinely analized.
Follow-ups after surgery were uneventful.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The appendix showed fat involutive aspects, with lumen pushed by large, expanded, well-delimited follicles, with thin/attenuated mantle zone and enlarged germinal centres, composed by admixture of small centrocytes to large centroblasts with only little evidence of polarization and rare macrophages with tingible bodies (no starry sky aspect).
Focal granulocytes in mucosa layer.

Immunophenotype

Immunistochemical stains performed showed a reactive profile of germinal centres: CD20+, CD10+, bcl6+, bcl2-, diffusely high Ki67 index (without significant polarization); rare CD3 lymphocytes in the germinal centres and rare IRF-4 cells.

Cytogenetics

None

Molecular Studies

PCR analysis: no evidence of clonal IgH rearrangement.

Proposed Diagnosis

Florid nodular lymphoid hyperplasia of the appendix

Interesting Feature(s)

Evident expansion in germinal centres with low numbers of tingible bodies macrophages and little polarization could be suspicion of follicular lymphoma of GI tract or large B-cell lymphoma with IRF-4 rearrangement; the negativity of IRF-4 stain and IgH gene rearrangement could clear out any doubt.

Lymphoid hyperplasia can be managed conservatively when identified early and is self-limiting but the DD with acute fase is difficult (maybe WBC count and other blood parameters could help).

References

Good DJ and Gascoyne RD. Hematol Oncol Clin N Am 23 (2009) 729–745.

Quintanilla-Martinez L et al. Virchow archives 2016 Feb;468(2):141-57.

Xu Y et al. American Journal of Roentgenology 2016. 206(1):189-194.

Martinez-Lopez A. Histopathology 2014, 65, 805–813.

Kaya A et al. Ulus Travma Acil Cerrahi Derg. 2022 Apr; 28(4): 434–439.

EA4HP24-LYWS-352

Atypical marginal zone hyperplasia in a child

Dr. Rebecca L. King, Dr. Ellen D. McPhail

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Case Description

The patient is a 2-year-old boy with recurrent tonsillitis and sleep apnea.

Bilateral tonsillectomy was performed.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

no

Details of Microscopic Findings

The tonsillar architecture is distorted but intact. There are prominent, well-spaced lymphoid follicles accompanied by expansion of the marginal zone. The germinal centers are composed of a heterogeneous cell population, contain numerous tingible-body macrophages, and show polarity, at least focally. The mantle zones are attenuated. The marginal zones are expanded by a fairly uniform population of small to medium sized lymphocytes with ample pale eosinophilic cytoplasm. This cell population shows prominent extension into the tonsillar crypts with prominent lymphoepithelial lesions.

Immunophenotype

There is a prominent population of CD20-positive B-cells within the germinal centers, mantle zones, marginal zones and lymphoepithelial lesions, accompanied by a lesser

population of small CD3-positive T-cells. The germinal center lymphocytes are positive for CD10 and BCL6, are centered on a nodular CD21-positive follicular dendritic cell meshworks, show variable (weak to negative) reactivity with IgD, and are negative for BCL2. MUM1 highlights scattered plasma cells. The germinal center B-cells, the marginal zone B-cells, and the plasma cells all show marked excess lambda expression, although a small subset of cells within these compartments express kappa immunoglobulin.

Cytogenetics

FISH negative for BCL2, BCL6, and IRF4 rearrangements.

Molecular Studies

No clonal IGH or IGK rearrangement.

Proposed Diagnosis

Atypical marginal zone hyperplasia

Interesting Feature(s)

The presence of an expanded marginal zone B-cell proliferation with follicular colonization and marked excess lambda light chain expression raises the possibility of marginal zone lymphoma. However, the absence of a clonal immunoglobulin gene rearrangement and absence of BCL2, BCL6, or IRF4 rearrangements by FISH would support a diagnosis of atypical marginal zone hyperplasia. The young patient age, anatomic site (tonsil), and skewed lambda light chain expression in the absence of features of clonality are all characteristic of atypical marginal zone hyperplasia.

EA4HP24-LYWS-367

A Young Man with a Single Cervical Lymphadenopathy

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Case Description

In 2015, a 22-year-old man presented with a palpable, firm, and mobile right supraclavicular lymphadenopathy. The symptoms began approximately four months prior, coinciding with a severe respiratory infection and headaches, although he did not have a fever. A CT scan identified a pathological lymph node measuring 3.2 x 2.5 cm in the posterior cervical triangle at the inferior right level (level V). Laboratory tests for *Treponema*, *Borrelia*, Epstein-Barr virus (EBV), and HIV were all negative. Cytological analysis of fine needle aspiration

(FNA) guided by ultrasound suggested reactive features. An excisional biopsy was subsequently performed.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded

Frozen Tissue Available

Yes

Details of Microscopic Findings

Microscopically, lymph node with predominantly preserved architecture. Of note is the presence of expanded germinal centers with hyperplasia of the marginal zone, progressive transformation of the germinal centers and follicle colonization. A polymorphous paracortical expansion with numerous activated B cells is also observed.

Immunophenotype

Immunohistochemical studies shows lymphocytes are positivite for CD20, CD79a and BCL2. Negative for CD3, CD5, CD10, IgD, and BCL6. Light chains are non-contributory. Ki67 approximately 30-40%.

Cytogenetics

None performed

Molecular Studies

- Clonality IGH studies (FRII and kappa chain) were **monoclonal**. FRIII was polyclonal.
- NGS studies (AmpliSeq Lymphoid Panel v2, ThermoFisher) identified a mutation in ***MAP2K1* / exon 3 NM_002755.4 c.361T>A p.Cys121Ser / VAF 5.15% / Likely Pathogenic**

Proposed Diagnosis

Pediatric follicular lymphoma with marginal zone differentiation (ICC)

Paediatric nodal marginal zone lymphoma (WHO-HAEM4R, WHO-HAEM5)

Interesting Feature(s)

1. Marginal zone lymphoma, pediatric variant, is a rare lymphoma, more common in males and typical of the head and neck region lymph nodes. It has an excellent prognosis
2. Our case exhibits marked characteristic histological features of marginal zone lymphoma, with scant morphologic traits suggestive of follicular lymphoma
    1. Surprisingly, our case showed moderate Ki67 expression (30-40%), contrary to the usual low levels seen in such cases
3. We identified a mutation in *MAP2K1*, a recurring genetic alteration in this disease
4. Recent studies suggest that pediatric follicular lymphoma and pediatric nodal marginal zone lymphoma may represent histological variations of the same disease. Despite no morphological overlap in our case, the recurrent MAP2K1 mutation, initially and typically associated with pediatric follicular lymphoma, could reinforce this notion - as mentioned in the recent publication *Salmeron-Villalobos, J. et al. (2022). A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile. Blood Adv, 6(16), 4661–4674. doi: https://doi.org/10.1182/bloodadvances.2022007322.*; thus, this could prompt reclassification of our case as "pediatric follicular lymphoma with marginal differentiation" according to the ICC classification.

5. Our patient underwent a watch-and-wait approach and remained disease-free; he is currently considered cured

EA4HP24-LYWS-374

Case of pediatric follicular lymphoma with marginal zone differentiation.

Dr. Anna Shestakova[1,2], Dr. Madhu Menon[1,2]

[1] University of Utah, Pathology, Salt Lake Cit, USA; [2] ARUP laboratories, Pathology, Salt Lake City, USA

Case Description
This is a 17-year-old male with a history of an enlarging right parotid mass without any additional symptoms.

Biopsy Fixation Details
10% neutral buffered formalin.
Frozen Tissue Available
Available.
Details of Microscopic Findings
This biopsy demonstrates uninvolved areas with unremarkable and sometimes small/atretic follicles along with partial effacement of lymph node with an atypical follicular proliferation that is composed of mostly centroblastic, large centrocytes and blastoid cells with abundant tingible body macrophages. Some areas demonstrate expansile, serpiginous germinal centers, while some areas demonstrate fragmentation of germinal centers and almost a "floral" pattern.

Sections of the lymph node show partially effaced architecture with intermixed sheets of cells with expansile and serpiginous germinal centers composed of centroblasts, large centrocytes, and monomorphic, intermediate sized lymphoid cells. The expanded germinal centers display attenuated mantle zones in some areas and some expanded zones around the germinal centers.
Immunophenotype
The expanded germinal centers appear positive for CD20, HGAL, MUM1, and dim BCL6; while negative for BCL2. The strong CD10-positive cells are mostly restricted to the germinal centers. Some areas demonstrate cells surrounding these follicles to be a mix of HGAL, BCL6 (dim), and MUM1 positive cells while the strong CD10+ cells correspond to the germinal centers. Few scattered cells are positive for EBV ISH. CD21 highlights an intact but expanded follicular dendritic meshwork. CD3 highlights small interfollicular T-cells.

CD30 highlights scattered intermediate-sized cells presumably immunoblasts. TDT highlights scattered immature cells. HHV8 and cyclin D1 are negative in the lymphoid cells. PD1 demonstrates TFH cells mostly seen at the periphery of the germinal centers or scattered throughout the germinal center. MIB1 proliferation is high within the germinal centers. Kappa and Lambda ISH demonstrate lambda restriction in the germinal centers. Concurrent flow cytometry aspirate showed a CD10+, lambda restricted, B cell population.

Cytogenetics

Karyotype - not done.

FISH studies were NEGATIVE for MYC, BCL2, BCL6, and IRF4 rearrangements.

Molecular Studies

DNA-based massively parallel studies of approximately 700 genes are pending.

Proposed Diagnosis

- ATYPICAL B-LYMPHOID PROLIFERATION WITH FEATURES OF PEDIATRIC FOLLICULAR LYMPHOMA.

Interesting Feature(s)

Pediatric follicular lymphoma with marginal zone differentiation.

EA4HP24-LYWS-414

IntestinalLarge B-cell lymphoma with*IRF4*rearrangement without IRF4 translocation.

Socorro Maria Rodriguez-Pinilla[1], Luis B. Santana[2], Isabel Colmenero[2], Francisco Javier Diaz de la Pinta[1]

[1] *Fundacion Jimenez Diaz, Pathology, Madrid, Spain;* [2] *Hospital Infatil Universitario Niño Jesus, Pathology, Madrid, Spain*

Case Description

A 5 year-old boy came to our hospital complining of vomiting and abdominal pain for a week. TAC images identified a round mass in the terminal ileum of 3,3 x 3,2 x 3,9 cm. An ileoctomy was performed. After diagnosis the patient received R-CHOP with locoregional recurrence of the disease and autologous haematopoyetic stem cell transplantation for consolidation. After 20 months of follow up he is safe and free of disease.

Biopsy Fixation Details

Paraffin embeded tissue. Formol 10%

Frozen Tissue Available

NO

Details of Microscopic Findings

A neoplastic proliferation of large atypical B cells involving the entire thinckness of the surgical specimen was found. Ulceration with destruction of epithelium was seen. No lymphoepithelial lesions could be identified. Cells were large with irregular nuclei and scant isolated nucleoli. Cytoplasm was clear and not prominent. Two different patterns of

infiltration were found one; nodular with a marginal growth pattern (10% of the neoplasm) and diffuse one (90% of the neoplastic proliferation). Residual dendritic cells were seen.

Immunophenotype

Neoplastic cells expressed CD20, CD10, BCL6 , MUM1, CD5 (focal and low), BCL2, PD1 (weak), kappa light chain and were negative for one Cyclin D1, CD30, CD3, LEF1, MNDA, MYC, and EBV (EBER). Isolated intense p53 positive cells were identified. The ki67 was positive in more than 80% of neoplastic cells.

Cytogenetics

Not done

Molecular Studies

Break apart FISH studies for IRF4, BCL6, BCL2, and MYC genes did not show any rearrangement.

NGS studies with a customized panel identified probably pathogenic mutation in TP53(p.Asn263LeufsTer82) (VAF 39%, frameshift) and others of unknown significance in IRF4(p.Cys19Tyr) (VAF 23%, missense) and CCND3 (p.Thr202Pro) (VAF 27%, missense) genes.

Proposed Diagnosis

Large B-cell lymphoma with *IRF4* rearrangement

Differential diagnosis with Diffusse transformation of either marginal zone B-cell lymphoma or follicular lymphoma should be done.

Interesting Feature(s)

No IRF4 rearrangement but a molecular profile similar to the one described in Large B-cell lymphoma with *IRF4* rearrangement cases.

Marginal patten of the nodular component

Location, desctibed but not frequent

CD5 expression (described)

PD1 expression

EA4HP24-LYWS-422

Early recurrence of a Pediatric Nodal Marginal Zone Lymphoma with a potential clonal evolution.

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Case Description

A 16-year-old female presented in october 2021 with an obstructive tumor of the right part of the oropharynx (tonsil) without cervical lymphadenopathy. There were neither B symptoms, nor biological abnormalities. Serology tests were negative. A tonsillectomie was performed. A Pediatric Nodal Marginal Zone Lymphoma was diagnosed (EAHP22 LYWS-1177). Chest-abdomen-pelvis CT scan was negative. Considered a localized disease no additional treatment was proposed and a watch and wait strategy was adopted.

After 15 months (february 2023) the patient presented a local recurrence with a bulky tumor of the right part of the oropharynx (tonsil and lingual tonsil) measuring 58x35x15 mm. A tonsillectomy was performed.

Biopsy Fixation Details

4% neutral buffered formol

Frozen Tissue Available

yes

Details of Microscopic Findings

Microscopic findings were similar in the 2 samples (2021 and 2023).

The normal tonsil architecture was replaced by numerous dark expansive and irregular follicles showing progressive transformation of germinal center-like pattern (PTGC-like). These irregular and disrupted follicles were surrounded by sheets of medium monocytoid and centrocyte-like cells. Large scattered transformed cells and few mitosis were present.

Immunophenotype

The immunostaining was similar in the 2 samples (2021 and 2023).

CD20 staining highlighted the follicules and inter-follicular areas. CD79a and PAX5 demonstrated a lower intensity in the inter-follicular areas. CD21 exhibited an expanded and disrupted follicular dendritic cells meshwork. IgD highlighted the PTGC-like pattern. There were no residual germinal center. Numerous CD3+/CD4+/PD1+ T-cells formed nodular and irregular aggregates in intra-follicular areas. There were no light chain restriction by ISH. The EBV ISH was negative.

Cytogenetics

not done

Molecular Studies

By PCR analysis (BIOMED-2), a clonal population was detected within a polyclonal background of B-cells for IGH (IGH FR1, IGH FR2, IGH FR3). This clonal population estimated to 10% of the B-cells population had an identical pattern (size products) in the 2 samples (2021 and 2023). There was no clonal rearrangement of TCRG.

NGS analysis (150 gene panel) was done on the 2023 sample and revealed 2 likely pathogenic variants : *CCND3* (NM_001760.5) p.(Q260Dfs*63) [vaf 3.4%, prof 1055x] ; *EP300* (NM_001429.4) p.(H2324Tfs*29) [vaf 2.6%, prof 117x] and 3 variants of unknown significance *POT1 (NM_015450.3) p.(P34H) [vaf 5%, prof 2856x] ; TNFRSF14 (NM_003820.4) p.(Y61D) [vaf 3%, prof 725x] ; SETD2 (NM_014159.7) Intron 12: c.5397+24G>A, p.(?) [vaf48.0%, prof 1345x]*

Subsequently, we decided to analyze the 2021 sample with the same panel and found only the *SETD2* variant which could fit with a germline variant.

Proposed Diagnosis

Early recurrence of a Pediatric Nodal Marginal Zone Lymphoma.

Interesting Feature(s)

The most common presentation of PNMZL is an asymptomatic lymphadenopathy involving head and neck region, but the tonsillar location has never been described. The majority of the patients has a localized stage I disease and shows a low rate of recurrence after conservative treatment. In our case the patient displayed an early recurrence with additional mutations that could correlate with a potential clonal evolution and the possibility of a continuous antigenic stimulation exerting a selective pressure. Increased intrafollicular PD1-positive TFH-cells commonly seen in adult NMZL have already been described in PNMZL such as in our case and could result from an antigenic stimulation of T-cells in germinal centers.

EA4HP24-LYWS-431

A pediatric-type follicular lymphoma with marked marginal zone differentiation

Prof. Falko Fend, Prof. Leticia Quintanilla-Martinez

Univ. Hospital Tübingen, Pathology, Tübingen, Germany

Case Description

19-year-old male without relevant clinical history. Left-sided cervical lymph node swelling was noted. An excisional biopsy was performed and submitted in consultation.

Biopsy Fixation Details

formalin fixation and paraffin embedding

Frozen Tissue Available

no

Details of Microscopic Findings

There is alteration of the lymph node architecture with large nodules, in part with germinal centers, in part reminiscent of progressive transformation of germinal centers, and with pale-staining marginal zones surrounding the nodules. There is little plasma cell differentiation. On higher magnification, the germinal centers are irregular and show a relatively monotonous proliferation of medium-sized blasts with focal starry sky pattern.

Immunophenotype

Immunohistochemistry demonstates large B-cell nodules with CD10+, MEF2B+, BCL6+ and BCL2neg germinal centers, in part with PTGC-like transformation with GC invasion by CD23+, IgD+ mantle zone cells. CD21 demonstrates expanded FDC networks. The GC are rimmed by IRTA1+ marginal zone B-cells There are few plasma cells without light chain restriction, and high numbers of reactive T-cells emphasizing the nodular pattern. MIB1 is high in the germinal centers, without polarization.

Cytogenetics

not available

Molecular Studies

Demonstration of B-cell clonality (IGH FR2 and FR3, BIOMED2 primers). Targeted NGS with a custom panel for BCL2-negative follicular lymphoma demonstrates a *MAP2K1* hotspot mutation: c.171G>C p. Lys57Asn with VAF of 9%.

Proposed Diagnosis

Pediatric-type follicular lymphoma with marked marginal zone differentiation

Interesting Feature(s)

Pediatric-type follicular lymphoma is a well-characterized germinal center-derived lymphoma with excellent prognosis lacking the *BCL2* translocation and showing a characteristic mutational profile. PTFL may show variable amounts of marginal zone differentiation as in this case, raising a DD of pediatric nodal marginal zone lymphoma (PNMZL), with which it shares clinical and other features. Recent data demonstrating significant overlap also in genetic features led to the suggestion that these both entities represent two ends of a spectrum of the same disease. Although PTFL and PNMZL have been retained in both current classifications, evidence may suggest to lump them together as PTFL w/wo marginal zone differentiation in the future.

Salmeron-Villalobos J, Egan C, Borgmann V, Müller I, Gonzalez-Farre B, Ramis-Zaldivar JE, Nann D, Balagué O, López-Guerra M, Colomer D, Oschlies I, Klapper W, Glaser S, Ko YH, Bonzheim I, Siebert R, Fend F, Pittaluga S, Campo E, Salaverria I, Jaffe ES, Quintanilla-Martinez L. A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile. Blood Adv. 2022 Aug 23;6(16):4661-4674.

Salaverria I, Weigert O, Quintanilla-Martinez L. The clinical and molecular taxonomy of t(14;18)-negative follicular lymphomas. Blood Adv. 2023 Sep 26;7(18):5258-5271.

EA4HP24-LYWS-435

Pediatric-Type Follicular Lymphoma in a Young Male with 10 Years of Follow-up and No Progression

Dr. Sarah Ondrejka, Dr. Meredith Nichols

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Case Description

A 21-year-old male developed an isolated, palpable enlarged left cervical lymph node in 2011. An excisional biopsy was performed. He was asymptomatic with no evidence of additional disease on PET and was observed. Ten years later he developed alopecia areata and vitiligo. As these immune-mediated phenomena can be seen in systemic lymphoma, this prompted review of the original pathology and imaging. The original biopsy specimen underwent additional testing.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The 2011 lymph node showed obliteration by numerous large, expansile, irregularly shaped follicles. The follicles lacked polarization and were comprised of haphazardly arranged centroblasts with occasional tingible body macrophages. In one of the blocks, areas with possible marginal zone differentiation were identified.

Immunophenotype

Flow cytometry showed an abnormal CD10+ monotypic kappa population comprising 20% of total events. Immunohistochemistry showed that cells within the expanded follicles expressed CD20, BCL6, CD10, and CD43, and were negative for cyclin D1, BCL2, and CD5. CD21 highlighted disorganized and expanded dendritic cell meshworks. Follicular Ki-67 proliferative index was 80-90% and accentuated the lack of polarization. Chromogenic in situ hybridization for EBV-encoded RNA (EBER) was negative. Ten years later, dual multiplex in situ hybridization for kappa and lambda showed a kappa predominance in a subset of follicles.

Cytogenetics

Not performed

Molecular Studies

B-cell clonality studies using BIOMED-2 PCR primers showed no evidence of a clonal rearrangement in immunoglobulin heavy chain or kappa loci. Ten years later, targeted next generation sequencing performed on extracted DNA from the 2011 biopsy identified a missense mutation in exon 2 of *MAP2K1* p.(Lys57Glu) with a variant allele fraction of 7%. Mutations in other genes including *CREBBP*, *EZH2*, *TNFRSF14*, and *KMT2D* were not detected.

Proposed Diagnosis

Pediatric-type follicular lymphoma

Interesting Feature(s)

In 2011, the differential diagnosis included pediatric-type FL, atypical follicular B-cell proliferation with features of PTFL, and florid reactive follicular hyperplasia with a clonal B-cell population by flow cytometry in an otherwise histologically reactive proliferation; it was cautioned that viral etiologies should be considered. A clone was not detected by PCR studies, but the histology was unusual with highly disrupted nodal architecture. The follicles lacked medium-sized blastoid cells described in PTFL, but clearly lacked polarity and harbored high-grade histology. Expression of CD43 and negative BCL2 were abnormal and a clear-cut abnormal population was identified by flow cytometry. In some areas, a peculiar marginal zone differentiation was identified. The patient's age was consistent with a diagnosis of PTFL. The patient had negative imaging studies, no symptoms related to lymphoma and received no radiation or immunochemotherapy. Look-back interpretation of the histology was the same ten years later, and it was possible to clearly see the kappa-restricted B-cell follicles with a dual multiplex stain. The presence of the *MAP2K1* variant, seen in up to half of PTFL and a subset of PNMZL cases, along with the absence of mutations commonly seen in conventional FL helped confirm PTFL. There was no evidence of lymphadenopathy on repeat comprehensive CT scans and no recommendation for the patient to continue seeing an oncologist.

EA4HP24-LYWS-447

Unusual Mutational Profile in Otherwise Typical Pediatric-type Follicular Lymphoma

Dr. Kavita Umrau[1], Dr. Jessica Muldoon[1], Dr. Aaron Phelan[2], PhD/MD Yukiko Kitagawa[1], Dr. Rohit Gulati[1], PhD/MD Kemin Xu[1], Dr. Kenneth Ofori[1], PhD/MD Magdalena Czader[1]

[1] Indiana University School of Medicine, Hematopathology, Indianapolis, USA; [2] Hardin Memorial Hospital, Pathology, Elizabethtown, USA

Case Description

22-year-old male with a history of SC disease presented with a left submandibular mass persistent for the past 8 years. CT scan demonstrated a 3.5 x 2.9 x 1.5 cm well-circumscribed heterogenous mass which showed no change in size over time, and no other sites of involvement on interval imaging studies. The patient was initially asymptomatic but subsequently developed dyspnea and dysphagia. A fine needle aspiration showed an atypical lymphoid proliferation, and a mass excision was performed. 3-year follow-up did not report any clinical evidence of disease.

Biopsy Fixation Details

Left submandibular mass, submitted fresh, serially sectioned, and representative portion submitted for flow cytometry. The remaining tissue was formalin-fixed and paraffin-embedded.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Lymph node architecture showed near complete effacement by large expansile serpiginous and focally fused follicles with attenuated mantle zones. Neoplastic follicles were composed of atypical medium-sized lymphocytes with blastoid cytomorphology, and tangible body macrophages. Dense fibrotic bands were noted in focal areas.

Immunophenotype

Neoplastic follicles were positive for CD20, PAX5, BCL6, CD10 and FOXP1, and negative for BCL2. PD1-positive lymphocytes were present at the periphery of neoplastic follicles. High proliferative activity without polarization was seen with Ki-67 immunostain (80% in neoplastic follicles).

Flow cytometry showed a small monoclonal B-cell population (10%) positive for CD19, CD20, CD22, CD10, and kappa light chain. Background polyclonal B-cells were also noted.

Cytogenetics

N/A

Molecular Studies

Clonal IgH gene rearrangement was identified by PCR (Primers FR1 and FR2)

Next-generation sequencing:
TNFRSF14 W12* (VAF 14.8%)
ARID1A R1461* (VAF 7.1%)
EZH2 Y646N (VAF 6.9%)
MAP2K1 (MEK1) F53V (VAF 5.7%)
Tumor mutational burden 8 mutations/Mb

Proposed Diagnosis

Pediatric-type follicular lymphoma

Interesting Feature(s)

The patient's presentation with an isolated cervical lymph node, clinically indolent course, and histologic and immunophenotypic features are typical of pediatric-type follicular lymphoma (PTFL); however, the 8-year duration of the localized lymphadenopathy, documented by repeat imaging, and genetic profile are unusual.

Genetic alterations include those seen typically in PTFL and conventional follicular lymphoma. The former include MAP2K1 (mitogen-activated protein kinase 1) and TNFRSF14 (TNF-superfamily cytokine receptor), which co-occur only in approximately 20% of PTFL cases.

Mutations in epigenetic modifier genes EZH2 (histone-lysine N-methyltransferase) and ARID1A (AT-rich interactive domain-containing protein 1A) are associated with usual follicular lymphoma. These mutations have been only rarely reported in PTFL including rare cases of adults with PTFL. However, on closer review, these cases may have represented usual follicular lymphoma; hence, the true incidence of epigenetic modifier genes mutations in PTFL is unknown.

Our patient showed both EZH2 and ARID1A and a higher mutational burden. It is conceivable that an accumulation of typically mutually exclusive and unusual mutations including involvement of epigenetic modifier genes may be related to a long duration of the disease.

EA4HP24-LYWS-466

Two pediatric cases of conjunctival atypical follicular hyperplasia with lambda light chain restriction

Dr. Shweta Bhavsar[1], Dr. Meredith Nichols[1], Dr. Anna Owczarczyk[1], Dr. Arun Singh[2]

[1] Cleveland Clinic, Pathology and Laboratory Medicine - Hematopathology, Cleveland, USA; [2] Cleveland Clinic, Ophthalmology, Cleveland, USA

Case Description

Case 1. An 11-year-old boy with a 3-month history of slowly growing salmon-colored left conjunctival lesion, otherwise asymptomatic and with no significant past medical history. Ophthalmic examination revealed bilateral conjunctival lesions, left greater than right, treated with prednisone with no improvement. An excisional biopsy was performed

for diagnosis. Post biopsy treated with anti-inflammatory eye drops (dexamethasone, neomycin & polymyxin B). Patient is doing well without evidence of lymphoproliferative disorder at 13 month follow up.Case 2. A 13-year-old boy with no significant past medical history presenting with an 8-month history of painless salmon-colored right conjunctival lesion, slowly increasing in size, clinically favored to represent benign HPV papilloma cyst. An excisional biopsy was performed for diagnosis. Patient is doing well without evidence of lymphoproliferative disorder at 13 month follow up.

Biopsy Fixation Details

Both formalin fixed

Frozen Tissue Available

No

Details of Microscopic Findings

The histologic sections from both the biopsies (case 1 & case 2) demonstrated similar histomorphologic features showing conjunctival mucosal fragments with unremarkable conjunctival epithelium with the subepithelial tissue showing a dense lymphoid proliferation composed of multiple hyperplastic follicles with ill-defined borders and irregularly shaped germinal centers with scattered tingible body macrophages, mitotic figures and germinal center polarization seen in some areas. The interfollicular areas were composed of small lymphocytes admixed with few histiocytes.

Immunophenotype

- Immunohistochemistry (case 1 & case 2): CD20 highlights numerous positive B cells in the hyperplastic lymphoid follicles. CD3 and CD5 highlight the T cells predominantly seen outside the B-cell rich follicles. CD10 and BCL6 highlight the irregularly-shaped germinal centers that are negative for Bcl-2. IgD highlights the robust mantle zones. The lymphoid cells are negative for cyclin D1 and TdT. CD21 highlights the expanded follicular dendritic cell meshworks. Ki-67 shows the expected high proliferative activity in the germinal centers. EBER-CISH was negative. Dual ultrasensitive chromogenic in situ hybridization for kappa and lambda-encoding mRNA showed germinal centers with a significant predominance of lambda positive cells. The IgD positive mantle zones showed polytypic lymphoid cells. The plasma cells were polytypic.
- Flow cytometric immunophenotypic studies (case 1 only): Showed an atypical lambda monotypic B-cell population (~24% of all cells) positive for CD10, CD19, CD20 and CD45. Many polytypic B cells were also present.

Cytogenetics

Case 1 only: Fluorescence in situ hybridization (FISH) studies performed on Case 1 were negative for *MYC*, *BCL2* and *BCL6* gene rearrangements.

Molecular Studies

Molecular PCR-based B-cell clonality studies (BIOMED 2) were performed in both cases with the following results:

- Case 1: Negative for clonal rearrangements in the immunoglobulin heavy (IGH) chain and immunoglobulin kappa (IGK) loci.
- Case 2: Positive for clonal rearrangements in the IGH gene (FR2 - 272 bp; DH1-6-J - 297 bp) and IGK gene (V-J - 144 bp; V-Kde - 284 and 287 bp)

Proposed Diagnosis

Conjunctival atypical follicular hyperplasia with lambda light chain restriction.

Interesting Feature(s)

- 2 pediatric cases with conjunctival lesions showing atypical reactive follicular hyperplasia with lambda light chain restriction akin to atypical marginal zone hyperplasia seen in pediatric patients.
- These could potentially be misdiagnosed as lymphomas and lead to overtreatment in pediatric patients.

Panel Diagnosis Session IV

Panel Diagnosis: Pediatric type follicular lymphoma (PTFL)

Case	Panel Diagnosis	Features
EA4HP24-LYWS-40	PTFL	clinical behaviour: residual/recurrent clonality performed by the panel: IgH monoclonal
EA4HP24-LYWS-67	cFL	BCL2+, low grade, trisomy 3 and 18
EA4HP24-LYWS-95	PTFL	Adult patient (41), inguinal MAP2K1 and TNFRS14 mutations
EA4HP24-LYWS-136	PTFL	adult patient (39), FOX1-positive, clonal
EA4HP24-LYWS-187	PTFL	extranodal (conjunctiva), no mutations, clonal
EA4HP24-LYWS-427	PTFL	adult patient (47), clonal
EA4HP24-LYWS-447	PTFL	8 year mass MAP2K1, TNFRSF14, EZH2, ARID1 mutations
EA4HP24-LYWS-466-2	PTFL	Clonal, conjunctiva, no NGS possibly due to lack of enough material

Panel Diagnosis: PTFL with MZ differentiation

Case	Panel Diagnosis	Features
EA4HP24-LYWS-13	PTFL mz	CD10+ Kappa restricted by FACS NGS by the panel: no potential driver mutation; MAP2K1 and IRF8 mutations were intronic
EA4HP24-LYWS-63	PTFL mz	TNFRSF14 mutation, IgH Monoclonal
EA4HP24-LYWS-64	PTFL mz	extra nodal; extrafollicular CD10+ cells MAP2K1 mutation
EA4HP24-LYWS-190	PTFL mz	Marginal zone differentiation, MUM1+ NGS by the panel:TNFRSF14 and MAP2K1 mutations were reported as potential drivers
EA4HP24-LYWS-202	PTFL mz	Typical case of overlapping features TNRFSF14, IRF8 mutations
EA4HP24-LYWS-345	PTFL mz	no mutations, IgH Monoclonal
EA4HP24-LYWS-367	PTFL mz	PNMZL; MAP2K1 mutation
EA4HP24-LYWS-374	PTFL mz	CD10+ Lambda restricted by FACS
EA4HP24-LYWS-430	PTFL mz	NGS by the panel: ACTB, GNA13 mutations
EA4HP24-LYWS-431	PTFL mz	MAP2K1 mutation

EA4HP24-LYWS-435	PTFL mz	No material for clonality; MAP2K1 mutation
EA4HP24-LYWS-1	PTFL mz	Core bx, difficulty in recognizing colonized follicles monoclonal
EA4HP24-LYWS-41	PTFL mz	Interfollicular growth pattern with increased Ki67 Clonal, Mutation in MEF2B
EA4HP24-LYWS-105	PTFL mz	IgK M, Different clonal picks in 2 bx; NGS by the panel: WHSC1 mutation only. Kappa-restricted B-cell population CD10+ by Flow
EA4HP24-LYWS-209	PTFL mz	Relapse, 10 year long lasting history; PTGC, Ki67 in interfollicular region, monoclonal
EA4HP24-LYWS-422	PTFL mz	Tonsil Early recurrence with clonal evolution aquired mut: pathogenic CCND3, EP300 and 3 variants of unknown significance POT1, TNFRSF14, SETD2 NGS by panel: There was no potential driver mutation reported; MAP2K1, IRF8, FOXO1 and EZH2 mutations were intronic. A missense variant of TNFRSF14. Clonal

Panel Diagnosis: Atypical MZ hyperplasia/PTGC/

Case	Panel Diagnosis	Features
EA4HP24-LYWS-36	Atypical Hyperplasia	No available material for NGS No clonality demonstrated
EA4HP24-LYWS-44	PTGC	No clonality demonstrated Tonsil NGS by the panel: no potential driver mutation
EA4HP24-LYWS-121	Atypical Hyperplasia	no clonality, no mutations
EA4HP24-LYWS-150	Atypical MZ Hyperplasia	Ileum Lambda restricted CD10+, polyclonal
EA4HP24-LYWS-314	Atypical MZ Hyperplasia	Rare in children and in LN; lambda chain restriction, Polyclonal, NGS by the panel: SLC1A5 mutation
EA4HP24-LYWS-348	Florid lymphoid HP	No clonality demonstrated; appendix
EA4HP24-LYWS-352	Atyipical MZ Hyperplasia	Tonsil, Polyclonal with lambda exces NGS by the panel:no potential driver mutation
EA4HP24-LYWS-466-1	Atypical MZ Hyperplasia	11M. Polyclonal. CONJUNCTIVA, NGS not possible

Panel Diagnosis: Marginal zone lymphoma of mucosa associated tissue and related

Case	Panel Diagnosis	Features
EA4HP24-LYWS-8	MALT with high grade transformation	Gastric MALT and transformation in pediatric patient with LN involvement
EA4HP24-LYWS-269	MALT cutaneous variant with IgG4	Intramuscular Monoclonal, no mutations

Panel Diagnosis: Plasma cell proliferations

Case	Panel Diagnosis	Features
EA4HP24-LYWS-254	Atypical plasma cell proliferation	Kidney, no rearrangement, no mutations, atypical phenotype
EA4HP24-LYWS-371	Extramedullary plasmacytoma	IgA+ How to rule out MALT lymphoma?

Panel Diagnosis: Testicullar follicular lymphoma

Case	Panel Diagnosis	Features
EA4HP24-LYWS-31	T-FL	Lack of 1p36 altERATIONS Additional mutations: IRF8, BTG1, ALMS1, ARID1A, ETS1,and KLHL6 prevalence of large centrocytes rather tan centroblasts
EA4HP24-LYWS-34	T-FL	Clonality by the panel: monoclonal. NGS: TNRSF14, EZH2, BTG1, BRCA2 mutations Growth pattern follicular and diffuse FISH IgH +in 17% of cells. Bcl2 R-
EA4HP24-LYWS-70	T-FL	LOH 1p36 but no loss detected by FISH; large prevalence of centrocytic cells; MEF2B+. Mut GNA13, RHOA, TNFRSF14

Panel Diagnosis: Others

Case	Panel Diagnosis	Features
EA4HP24-LYWS-304	Follicle center lymphoma of the lower genital tract	Vulva CD23+
EA4HP24-LYWS-414	Large B-cell lymphoma with IRF4	Intestinal Lack of IRF4 r, P53 MUT IgH unbalanced rearrangement by the panel

LYMPHOMA SESSION V:
Lymphoid neoplasms with indolent behaviour (clonal lymphoproliferations with indolent behaviour)

Oral Presentations

EA4HP24-LYWS-22	Primary Cutaneous Marginal Zone Lymphoproliferative Disorder
EA4HP24-LYWS-47	Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder (lymphoid neoplasms, typically, with indolent behavior), EBV positive, with transformation to plasmablastic lymphoma
EA4HP24-LYWS-303	Primary cutaneous marginal zone lymphoproliferative disorder with an associated clonal CD4-positive T-cell population
EA4HP24-LYWS-246	Indolent T-lymphoblastic proliferation of the parotid gland
EA4HP24-LYWS-344	A Synchronous Diagnosis of a Muscular Lymphoma-like T-cell Proliferation in a Patient with Tonsillar Squamous Cell Carcinoma: Coincidence or Causality?
EA4HP24-LYWS-461	An unusual indolent clonal T-cell LPD disorder of the GI tract
EA4HP24-LYWS-364	Indolent T-cell-lymphoma of the gastrointestinal tract with extraintestinal dissemination prior to histological and clinical progression
EA4HP24-LYWS-317	Follicle Center Lymphoma of the Lower Female Genital Tract
EA4HP24-LYWS-338	Follicular extranodal lymphoma with *BCL2* and *MYC* rearrangement.
EA4HP24-LYWS-38	46-year-old woman with *in situ* B-cell neoplasm with *MYC* rearrangement

EA4HP24-LYWS-22

Primary Cutaneous Marginal Zone Lymphoproliferative Disorder

Dr. Alma R. Oskarsdottir, Dr. Rebecca L. King

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Case Description

A 13-year-old, healthy male presented for evaluation of multiple cutaneous lesions. Two years prior to this presentation, he was evaluated for subcutaneous nodules involving both upper extremities. A biopsy from a left upper arm lesion was diagnosed as cutaneous lymphoid hyperplasia. During the current evaluation, physical examination revealed pink-red, circular nodules involving his left shoulder, arm, chest and back. The nodules were less than 1 cm in size. They were soft and nontender, without fluctuance and drainage. The patient did not report any itching associated with the lesions and no specific triggers were identified.

Biopsy Fixation Details

Formalin.

Frozen Tissue Available

None.

Details of Microscopic Findings

Biopsy of skin involved by a dense lymphoid infiltrate involving the superficial dermis with focal extension into the subcutaneous fat. The infiltrate is composed of small lymphocytes with admixed plasma cells located primarily just beneath the epidermis and in the deep part of the lesion. The lymphocytes have round nuclei, condensed chromatin and scant to moderate amounts of pale cytoplasm. No significant epidermotropism is seen. Small reactive secondary follicles are present toward the base of the lesion.

Immunophenotype

The lymphoid infiltrate is composed of CD20 positive B-cells admixed with more abundant T-cells and peripherally located plasma cells. The neoplastic B-cells are negative for CD10 and BCL6. CD10 and BCL6 highlight reactive germinal centers. The plasma cells are kappa restricted, express IgG and are negative for IgM and IgG4. The T-cells show a normal ratio of CD4:CD8 and expression of CD5 and CD7 is preserved. CD30 stains occasional immunoblasts. EBV-ISH is negative.

Cytogenetics

Not applicable.

Molecular Studies

Clonal immunoglobulin gene rearrangement.

No clonal T-cell receptor gene rearrangement.

Proposed Diagnosis

Primary cutaneous marginal zone lymphoproliferative disorder.

Interesting Feature(s)

Despite the patient´s young age, the combined findings are in keeping with the diagnosis of a primary cutaneous marginal zone lymphoproliferative disorder/lymphoma (PCMZL). In the 5th edition of the WHO, these lesions are classified as indolent lymphoma with marginal zone lymphoma-like features. However, in the 2022 International Consensus Classification the entity was downgraded to a lymphoproliferative disorder based on its indolent behavior. Both groups have separated PCMZL from other MALT lymphomas due to their unique features.

This is a classic example of this entity, exhibiting the typical features seen in the IgG-positive subtype. Two defined subtypes of these lesions are the heavy chain class-switched and non-class-switched forms. In our case, the plasma cells expressed IgG, and it thus falls into the more common category of heavy chain class-switched cases. The long-standing clinical history of cutaneous lesions in our patient is consistent with the characteristic indolent behavior of this entity. Numerous T-cells can be present, especially in class-switched cases. The T-cell infiltrate can potentially obscure the neoplastic B-cells and T-cell neoplasms are important differential diagnoses. Our case did have an abundant T-cell infiltrate, however aberrant T-cell phenotype or clonal T-cell receptor gene rearrangement were not identified, supporting the reactive nature of the T-cells.

EA4HP24-LYWS-47

Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder (lymphoid neoplasms, typically, with indolent behavior), EBV positive, with transformation to plasmablastic lymphoma

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Case Description

61 yo male, h/o hemochromatosis and psoriatic arthritis, presented May 2021 with nodular skin lesions (bilateral forearms and lower extremities). Biopsy left forearm lesion: PCMZL/LPD. PET: numerous cutaneous and subcutaneous nodules, no adenopathy or visceral lesions. Bone marrow (BM) biopsy unremarkable. Treated with localized radiation therapy.

New extremity skin nodules 2022. PET scan: widespread cutaneous progression; no adenopathy or internal organ involvement. October 2022 right thigh nodule biopsy:

increased large cells compatible with transformation. Rituxan started early 2023 without response, switched to Obinutuzumab / Bendamustine end of March.
May 2023, enlarging nodules on back and posterior leg, received radiation with improvement. Progressive disease September, skin biopsy left shoulder and left posterior knee: plasmablastic transformation. PET: multiple nodular FDG intense regions (max SUV 27.1): subcutaneous, GI tract, left external iliac and inguinal lymph nodes. BM biopsy unremarkable. Treatment changed to EPOCH + Velcade.

Biopsy Fixation Details

Formalin

Frozen Tissue Available

na

Details of Microscopic Findings

BM 2021 and 2023 unremarkable (morphology, IHC, flow cytometry)
May 2021, Left upper arm: Nodular, predominantly dermal lymphoplasmacytic infiltrate often surrounding adnexal structures, composed of small, mature T cells and B cells (CD20 and BCL2 positive; negative for CD10 and BCL6) with condensed chromatin and more numerous plasma cells (kappa restricted, IgG positive). EBER positive, Ki-67 proliferative index low, <10%.
October 2022, Right thigh: Nodular dermal infiltrate associated with adnexal structures, extending into the subcutaneous tissue. Lymphoid infiltrate CD20 positive, contains small, and more numerous larger cells with vesicular chromatin and variably prominent nucleoli with associated lambda restricted plasma cells. EBER positive, Ki-67 proliferative index high at 60-80%.
September 2023, Left shoulder and left posterior knee: Predominantly diffuse dermal and subcutaneous lymphoid infiltrate composed of large cells with vesicular chromatin, prominent nucleoli and variable amounts of cytoplasm. Positive for CD138, MUM1, MYC (>60%), CD30 (patchy, 60%), PD-L1, CD79a (small subset), Ki-67 (>90%), EBER, LMP1, subset BCL6, very small subset IgG, kappa, and negative for CD5, CD10, CD19, CD20, CD23, BCL1, BCL2, IgM, IgA, ALK, PAX5, KSHV, EBNA2.

Immunophenotype

see above

Cytogenetics

BM 2021, 2023: normal karyotype.
SKIN 2023 FISH:
Negative: MYC, MYC/IGH, BCL6, BCL2 rearrangement
Positive: monosomies 18/18q21, 3/3q27, 8/8q24

Molecular Studies

BM 2023: *DNMT3A* (c.1937-1G>A) 46%; *TET2* (c.1133del; p.G378fs*49) 45%; *TET2* (c.3008G>A; p.W1003*) 39%.
May 2021
DNMT3A (c.1937-1G>A) 24%; *TET2* (c.1133del; p.G378fs*49) 32%; *TET2* (c.3008G>A; p.W1003*) 29% (Tumor burden: 70%)
October 2022

DNMT3A (c.1937-1G>A) 32%; *TET2* (c.1133del; p.G378fs*49) 35%; *TET2* (c.3008G>A; p.W1003*) 35% (Tumor burden: 60%)
IgH/IgK clone detected
September 2023
DNMT3A (c.1937-1G>A) 43%; *STAT3* (c.1919A.T; p.G378fs*49) 41%; *TET2* (c.1133del; p.G378fs*49) 46%; *TET2* (c.3008G>A; p.W1003*) 43% (Tumor burden: 80%)
IgH/IgK clone detected, similar to 2022

Proposed Diagnosis

EBV positive PCMZL/LPD (2021), with transformation to large cell (2022), and plasmablastic lymphoma with dissemination (2023).

Interesting Feature(s)

EBV positive PCMZL/LPD is uncommon, expression of different light chains at different time points unusual, transformation to aggressive lymphoma rare and may be evolving from clonal hematopoiesis.

EA4HP24-LYWS-303

Primary cutaneous marginal zone lymphoproliferative disorder with an associated clonal CD4-positive T-cell population

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Case Description

A 37-year-old, otherwise healthy man presented with multiple painless and non-itching erythematous plaques on his left shoulder and upper back, which had developed approximately two years earlier. An excisional biopsy of one lesion was performed (submitted). A staging CT scan revealed no additional manifestations. The bone marrow and peripheral blood were uninvolved by histology and/or flow cytometry. Treatment consisted of an excision of all lesions without adjuvant radio- or chemotherapy. At his most recent follow up 20 months later, the patient showed no signs of recurrence.

Biopsy Fixation Details

Formalin-fixed tissue.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The excisional biopsy showed a dense lymphatic infiltration predominantly located in the superficial dermis with a diffuse to vaguely nodular pattern with only rare intraepithelial

lymphocytes. In some areas, there was an extension into the deeper dermis with a periadnexal and perivascular distribution. Reactive germinal centers were not observed. Cytologically, the infiltrate consisted primarily of small- to medium-sized lymphocytes, along with only scattered larger cells as well as plasma cells, histiocytes, and eosinophils.

Immunophenotype

CD20showed small B-cells distributed diffusely and in small aggregates, which otherwise had a CD5-, CD10-, BCL6-, IRTA1-, CD23+/- phenotype. CD23 and CD21 revealed only isolated follicular dendritic cell meshworks. MUM1 stained the plasma cell component, the majority of which was IgG and IgG4 positive and predominantly showed a kappa light-chain expression, indicative of a light-chain restriction. CD3 demonstrated numerous T-cells, which overall were more abundant than the B-cells. CD4 and CD8 in turn showed a predominance of CD4+ T-cells. CD2 and CD5 expression was retained in the T-cells, while CD7 was partially lost. A subset of lymphocytes, many of them larger and/or atypical, showed PD1, ICOS and partial CXCL13 positivity, consistent with T-cells with a follicular helper (TFH) phenotype. BCL6 also showed positive cells of mostly medium size, likely corresponding to the same population. The MIB-1 proliferation index was low.

Cytogenetics

Not done.

Molecular Studies

Biomed-2 immunoglobulin heavy chain clonality analysis demonstrated a clonal B-cell receptor rearrangement with clonal products of 343 bp (FR1) and 144 bp (FR3). T-cell receptor (TCR) gamma and beta clonality analysis also showed a clonal product of 259 bp (TCR beta, Tube A). Targeted next-generation sequencing of 78 genes frequently altered in lymphoma did not reveal pathogenic mutations.

Proposed Diagnosis

Primary cutaneous marginal zone lymphoproliferative disorder/primary cutaneous marginal zone lymphoma (ICC 2022/WHO 5th edition) with an associated clonal CD4-positive T-cell population.

Interesting Feature(s)

The simultaneous presence of a clonal B-cell population with an IgG4+ plasma cell component and a clonal T-cell population expressing TFH markers poses a diagnostic challenge and illustrates the oftentimes overlapping features of primary cutaneous marginal zone lymphoproliferative disorder/lymphoma (PCMZL) and primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder (Donzel *et al*., Sci Rep 2023). In fact, Obiorah *et al.* (Am J Surg Pathol 2023) recently published a series of similar cases and proposed clinicopathological and molecular criteria to aid in the differential diagnosis, which, when applied to this case, support the diagnosis of PCMZL. This case also emphasizes the indolent behavior of PCMZL.

EA4HP24-LYWS-246

Indolent T-lymphoblastic proliferation of the parotid gland

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Case Description

- 86-year-old woman
- No significant medical history, except a swelling of the left parotid gland that occurred 2 years ago, and has recently quickly increased in volume (tumor size: 4 cm), leading to its resection
- The **parotidectomy** has been referred for expertise (proposed diagnosis ´´: lymphoma NOS)

Evolution:

- Work-up and staging: Blood cell counts and bone marrow aspirates were unremarkable.
- No other tumor and no biological abnormality were found. The patient was in good shape
- PET scanner: negative
- A wait and watch strategy was applied
- No recurrence and no sign of disease with **a follow-up of 16 month**s after surgery

Biopsy Fixation Details

Formalin 4%

Frozen Tissue Available

No

Details of Microscopic Findings

The glandular parenchyma is massively infiltrated by diffuse sheets of small lymphoid cells, with round and pretty regular nuclei, sometimes displaying a moderately immature chromatin. There was no major atypia.

Mitotic figures are present.

A few follicles with germinal centres are seen at the periphery of the lesion. The epithelial structures are dissociated and partly invaded by the lymphoid infiltrate. They show occasional hyperplastic features or serous metaplasia.

Immunophenotype

- Relatively homogeneous expression of pan-T cell markers (CD3+ CD2+ CD5+^{weak} CD7+)
- CD4+/CD8+ double-positive profile
- Diffuse expression of immaturity markers TdT+ and CD1a+
- High proliferation index (Ki67 > 95%)
- EBER negative

- The rare B-cell follicules display a classic CD10+/BCL2- profile of reactive GCs

Cytogenetics

ND

Molecular Studies

- Clonality analysis (BIOMED-2) performed on the parotidectomy FFPE sample: **Polyclonal** pattern for *TCRB* and *TCRG* genes.
- NGS ongoing

Proposed Diagnosis

Indolent T-lymphoblastic proliferation of the parotid gland

Interesting Feature(s)

- This case highlights the importance of morphological clues (no major atypia) that can hint at the diagnosis of indolent lymphoblastic proliferation rather than T-lymphoblastic lymphoma, despite similar high proliferation index and immature phenotype.
- It points out the importance of clinico-biological informations and clonality analysis to assess the differential diagnosis
- Cases of parotid gland involvement by indolent lymphoblastic proliferation are rare (4% among all localizations). Previous cases were described in association with acinic cell carcinoma (absent in the present case).
- Haematopathologists should be aware of this lesion, which can lead to a misdiagnosis of malignancy (especially if clonality is not performed)

EA4HP24-LYWS-344

A Synchronous Diagnosis of a Muscular Lymphoma-like T-cell Proliferation in a Patient with Tonsillar Squamous Cell Carcinoma: Coincidence or Causality?

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Case Description

We present the case of a 62-year-old woman diagnosed in 2020 of a locally advanced, poorly differentiated HPV and EBV independent squamous cell carcinoma (SCC) of the oropharynx. During the staging, she presented with multifocal muscular hypermetabolic deposits in PET/CT scan, suggestive of metastasis. The patient neither experienced muscular weakness nor had abnormal laboratory findings. No clinical history of COVID.

Multiple muscle biopsies were performed which showed a monoclonal atypical T-cell infiltrate, consistent with a PTCL, NOS.
The clinicians decided to treat the SCC with local radiotherapy and cisplatin-based chemotherapy, instead of starting hematospecific treatment. After two cycles, the muscle lesions disappeared and the multidisciplinary team opted for a close follow up instead of active treatment.
Over the two years between the diagnoses and her death, the patient developed nodal and lung metastasis of the SCC that required multiple lines of chemotherapy. During this time, there was no relapse of the so-called lymphoma.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

Yes.

Details of Microscopic Findings

The slides show an atypical lymphoid proliferation infiltrating striated muscle fibers that do not display necrosis or angiocentricity. This infiltrate is constituted of medium sized lymphocytes with a broad, clear cytoplasm and irregular nuclei.
There was no evidence of said infiltrate in the samples of the SCC.

Immunophenotype

Positive for CD3, CD8, CD2, CD7, TIA1, Granzyme B. CD5 and BF1 partially positive.
Negative for CD56, CD30, EBERs.
ki67: 75%.
Flow cytometry: memory CD8+ T-cells.

Cytogenetics

Not performed.

Molecular Studies

Gamma and beta TR clonality was demonstrated in all the samples.
NGS Ampliseq Lymphoid panel v2, ThermoFisher: absence of pathogenic mutations.

Proposed Diagnosis

Reactive clonal CD8+ T cell infiltrate affecting multiple muscle groups.

Interesting Feature(s)

Our case exemplifies a clonal proliferative T-cell infiltrate resembling a lymphoid neoplasm. Such instances have been documented in regressed cutaneous neoplasms, typically manifesting as a local tumor-related reaction. However, in contrast to prior observations, our case displays a more systemic dissemination.
Clonal CD8+ T cell populations with a memory cell phenotype may also be present in the tumor microenvironment as tumor infiltrating lymphocytes or in the lymph nodes draining the tumor. The presence of these cells is associated with enhanced disease control and a more favorable prognosis. Nevertheless, there is a notable absence of evidence indicating similar proliferations occurring distantly from the tumoral mass. Our case did not show an increase in memory CD8 lymphocytes in the diagnostic biopsy of the SCC or in the lymph node metastasis.
The clonal expansion of CD8+ T cells has been described in autoimmune disorders, like

polymyositis, which may precede or coincide with solid neoplasms as a paraneoplastic syndrome. However, the absence of muscle weakness or an elevation of muscle enzymes in our patient goes against this diagnosis.
Diffuse infiltrative lymphocytosis syndrome (DILS) is a condition primarily observed in HIV patients. It is characterized by a monoclonal expansion of CD8+ T-cells. This expansion is specific to certain MHC molecules, indicating a restricted immune response. Our case does not meet the criteria for the DILS diagnosis.
Given the concurrent occurrence of the squamous cell carcinoma and the lymphoid infiltrate we hypothesize that the latter might signify a systemic hyperimmune reaction directed towards circulating tumoral antigens.

EA4HP24-LYWS-461

An unusual indolent clonal T-cell LPD disorder of the GI tract

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Case Description
A 74-year-old man presented in 2022 with melena revealing a single polypoid lesion in the jejunum. There was no lymphadenopathy. In August 2023, he underwent surgical resection. The patient had a past of surgical correction of an abdominal hernia. He had no clinical symptoms of enteropathy. He was followed since 2015 for a monoclonal B-cell lymphocytosis (MBL) (0.3x109/L clonal B cells; Matutes score 4/5).
At the time of jejunal resction, the lymphocyte count was normal, and no phenotypically aberrant T-cell population was detected. Serology for anti-endomysium, gliadin, transglutaminase IGA antibodies was negative. The patient had HLADQA1°05 haplotypes. Staging (PET-CT, peripheral blood) was negative. The patient is doing well without therapy and without disease 18 months after diagnosis, and 6 months after surgery.
Biopsy Fixation Details
Formalin
Frozen Tissue Available
Yes
Details of Microscopic Findings
The mucosa was infiltrated by a monotonous dense non-destructive population of small lymphocytes without significant atypia, which spread on the whole mucosa but also variably infiltrated the different layers of the intestinal wall. There were a few eosinophils. A

few B-cell nodules were present. An increase of intraepithelial intestinal lymphocytes was present, better emphasized by immunohistochemistry. Depending on areas, mild villous atrophy was observed. In one area, a 1-cm fibrotic nodule of undetermined significance was observed in the submucosa.

Immunophenotype

Besides B-cell follicles (CD20+, PAX5+), the diffuse infiltrate was composed of small T lymphocytes with a normal CD3+, CD2+, CD5+, CD7+ phenotype, with predominance of CD8+, TIA1+/GrB-/perf-, CD56-, CD57- cells. They did not express the NK-cell associated molecules KIR3DL2 and NKP46. They were TCRdelta-, CD30-, CD25-. A significant proportion of these cells was CD103+, diffusely infiltrating the whole intestinal wall. IHC evidenced increased IELs with a normal CD8+, CD103+ phenotype. The Ki67 proliferation rate was very low (<5%). EBV was negative (EBER ISH).

Cytogenetics

None

Molecular Studies

- Clonality analysis (TRB and TRG): clonal T-cell population (and absence of B-cell clone)
- NGS: NGS study found a unique *DNMT3A* mutation (c.G2120A p.G707D, 5,2%), possibly related to clonal hematopoiesis. There was no mutation identified in *CD28; IDH2; JAK1; JAK3; MSC; PLCG1; RHOA; SETD2; STAT3; STAT5B; TET2; TNFRSF1B; TP53; VAV1*.
- WES and LD-RTPCR (fusions panel incl. *JAK2-STAT3*) are pending.

Proposed Diagnosis

Indolent T-cell lymphoma of the GI tract (WHO-HAEM5, 2022)

Indolent clonal T-cell lymphoproliferative disorder of the GI tract (ICC, 2022),... Despite unusual features incl. intraepithelial component and CD103 expression, partial villous atrophy, diffuse spreading into the wall of the intestine and abundant reactive infiltrate (B-cell follicles) .....

Interesting Feature(s)

- EATL or type II RCD appears very unlikely (absence of context of enteropathy, small CD8+ T cells infiltrate with a non-activated cytotoxic phenotype, absence of expression of NK-associated molecule, absence of mutation in *JAK1, STAT3).*
- MEITL does not fit with cytological appearance, absence of CD56, GrB or perforin, very low Ki67 index and the genetic profile (absence of both *SETD2* and *STAT5B* mutations);
- A secondary infiltration of the jejunum by another T-cell lymphoma/leukemia such as T-LGL cannot be retained (absence of LGL in the PB, inadequate phenotypic profile)
- A diagnosis of “Intestinal T-cell NOS”, could be discussed but the small cell morphology without destruction of the glands and low ki67 favour indolent clonal T-cell LPDs of the GI tract.

EA4HP24-LYWS-364

Indolent T-cell-lymphoma of the gastrointestinal tract with extraintestinal dissemination prior to histological and clinical progression

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Case Description

07/2011: A 39-year-old male patient had a routine gastro-duodenoscopy. Initial diagnosis: Unusual B-cell-rich infiltrate without detectable clonal expansion.

11/2011: Detection of retroperitoneal lymphadenopathy and splenomegaly. Since a clonal expansion of T-cells in the lymph node (LN) and gastroduodenal (GI) specimens was identified, a re-evaluation led to the diagnosis of an unclassified clonal T-cell proliferation with aberrant CD20 expression. No bone marrow (BM) infiltration was present. Watch-and-wait approach.

06 and 08/2012: Persistent GI infiltrates and unremarkable BM.

07/2013: Persistent GI infiltrates.

03/2014: Suspicious lymphocytosis (16.000/µL) with pathological CD4/CD8 ratio and increased LDH. Demonstration of the clonal T-cell population in BM and peripheral blood (PB). Persistent GI infiltrates.

09/15: Disease acceleration with prominent lymphocytosis (62.000/µL), and parapancreatic bulk. 16 weeks of anti-CD52 treatment resulted in BM clearance and good overall response (04/2016).

06/2016: Focal GI infiltrates.

07/2016: Patient presented with visual disturbances and low back pain. Imaging revealed a right orbital mass, progressive disseminated lymphadenopathy, bilateral pulmonary infiltrates and osseous lesions. Biopsy from a sacral lesion showed progression to a clonally related aggressive T-cell lymphoma. Treatment with DHAP and intrathecal Cytarabin, Cortison and MTX led to a good response. Patient was lost to follow-up.

Biopsy Fixation Details

formalin

Frozen Tissue Available

No

Details of Microscopic Findings

GI biopsies: Dense diffuse and focal nodular infiltrate of small- to medium-sized lymphocytes with round or mildly irregular nuclei, fine chromatin, indistinct nucleoli and moderate cytoplasm in the lamina propria with extension into the submucosa without significantly increased intraepithelial lymphocytes.

Retroperitoneal LN: Monotonous lymphocytic infiltrate in the expanded interfollicular zones.
BM trephine: Interstitial infiltrate (30% of cellularity) by small- to medium sized lymphocytes also present in the PB.
Os sacrum: Diffuse infiltrate of large cells with polymorphic large nuclei containing small nucleoli.

Immunophenotype

The T-cell infiltrates in GI, LN and BM showed an expression of CD3, CD2, CD5, CD7, CD4, both T-cell receptor (TCR) β and γ chains, CD57 and in a variable percentage of PD1 and ICOS as well as aberrant CD20 and CD79a expression. No expression of CD8, perforin, granzyme B, TIA1, CD56, CD30, TCL1, FOXP3, TdT. EBER-in situ hybridization was negative. Variable Ki67-index (10-20%), focally up to 30%.
The large transformed lymphocytes in the osseous lesion showed an identical immunophenotype except for absence of CD20 expression. Ki67 90%.

Cytogenetics

N.d.

Molecular Studies

Analysis for TCR γ chain gene rearrangements revealed identical biallelic amplificates in all samples (GI biopsies from 2011, 2012, 2014, LN from 2012, BM and peripheral blood from 2014 and the last osseous lesion).
An in-house NGS-Panel analysis of the LN from 2012 and the last biopsy with the aggressive T-cell lymphoma revealed in both samples identical mutations in JAK1# (Exon 15; c.2097_2098insG; p.Ser700Glufs*9) and in TET2* (Exon 11; c.5260G>C; p.Gly1754Arg).# Frameshift mutation not yet described; *Variant of unknown significance.

Proposed Diagnosis

Indolent T-cell lymphoma of the GI tract with progression to aggressive T-cell lymphoma

Interesting Feature(s)

- Not previously reported immunophenotype
- Extraintestinal dissemination prior to progression
- Relatively early occurrence of histological and clinical progression
- Stable mutational profile at histological progression

EA4HP24-LYWS-317

Follicle Center Lymphoma of the Lower Female Genital Tract

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Case Description

We received a consultation of a 22-year-old female presented with persistent abnormal uterine bleeding with suspected cervical atypia. A PET/CT examination showed uptake in the vagina and lower tract of the uterus, with mild diffuse uptake in the vertebrae and iliac bones. MRI of the skull and spine showed no abnormalities. Bone marrow biopsy was negative for lymphoma. Peripheral blood flow cytometry was negative for abnormal lymphocyte populations.

Biopsy Fixation Details

Cervical Loop Electrosurgical Excision Procedure (LEEP), submitted for formalin fixation and embedded in paraffin.

Frozen Tissue Available

No

Details of Microscopic Findings

Sections show cervical mucosa involved by lymphoma. The overlying cervical epithelium was intact (figures 1A and 1B, 2X and 4X). The lymphoma shows predominantly a follicular pattern (figure 1C, 10X), and focally a diffuse growth pattern (figure 1d, 10X). The lymphoma cells in the follicular and diffuse patterns are predominantly large centrocytes, with occasional centroblasts (figures 1E and 1F, 20X and 40X respectively).

Immunophenotype

Immunohistochemical studies (figure 2) revealed the lymphoma cells to be positive for CD20 and BCL6, and negative for CD3, BCL2 and CD10. Ki67 shows an overall proliferation rate of approximately 50-60% in the lymphoma cells. The lymphoma cells were also negative for CD30 and MUM-1. EBER was negative.

Cytogenetics

FISH studies were performed in our institution and were negative for *IGH::BCL2* gene rearrangements. However, a subset of the tumor cells shows one extra copy of *IGH* and *BCL2.BCL6* was reported to be rearranged, and *MYC* was reported not to be rearranged or amplified.

Molecular Studies

Next generation sequencing was performed in our institution (EndLymphoma Assay) and showed the following somatic mutations: *TNFRSF14* (c.551+2T>G, VAF =18%), *S1PR2* (c.992C>T, VAF=39%), *IGLL5* (c.43G>A, VAF =16%) and *EZH2* (c.1936T>A, VAF<5%).

Proposed Diagnosis

Follicle center lymphoma of the lower female genital tract.

Interesting Feature(s)

Follicle center lymphoma of the lower female genital tract is a rare distinct subtype of follicular lymphoma, typically manifesting in the uterine cervix and vagina, that has been recently further characterized by Saksena *et al.* (American Journal of Surgical Pathology, 2023, 47, 409-419). Despite often containing a significant proportion of large B cells, it does not meet criteria for diffuse large B-cell lymphoma. Clinically, this neoplasm tends to be characterized by localized disease with a low-risk of dissemination and it has been suggested that it shares several characteristics with primary cutaneous follicle center lymphoma.

EA4HP24-LYWS-338

Follicular extranodal lymphoma with BCL2 and CMYC rearrangement.

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Case Description

A 45-year-old female with a tumor presented 2 months ago in the ventral mucosa of movable tongue that prevented her from eating and speaking properly. She had no fever or flu-like symptoms in previous months. The patient reports a 5kg weight loss without cold sweats. Physical examination showed no palpable adenopathy or organomegaly.

The lingual tumor was removed without complications. This allows her to regain his eating habits and speech.

The blood test has showed normal levels of LDH and B2, iron-deficiency anemia, normal quantification Ig, no serum monoclonal spike. Polyclonal IgH rearrangement in peripheral blood.

No enlarged lymph nodes were identified in the CT scan. Contrast enhancement of both sublingual and submandibular glands. Nodular hypodense lesion of 12 mm in diameter in the left submandibular gland with SUVmax 7.79 on PET/TC. There was no significant hypermetabolic lymphadenopathy.

During the following 9 months the submandibular nodule grows up to 2cm and an excision biopsy was decided.

No bone marrow study was performed.

Biopsy Fixation Details

Lingual and submandibular gland biopsies fixed in 10% neutral buffered formaldehyde.

Frozen Tissue Available

No frozen tissue available

Details of Microscopic Findings

Lingual and submandibular gland biopsy: Muscular tissue and salivary gland, respectively, infiltrated by proliferation of abnormal follicular structures with lack of tangible body

macrophages, polarization and well-formed mantle zone. No diffuse sheets of lymphocytes. The neoplastic follicles showed frequent centroblasts. No inmunoblast like morphology were seen.

Immunophenotype

The lymphoma cells expressed CD20 and germinal center associated antigens (BCL6 and CD10) with co-expression of BCL2 and CD23. There were negative for CD5, cyclinD1, p53, MUM1, EBER and there were polytypic plasmatic cells. The proliferative index by ki67 was uniformly increased. The cmyc by immunohistochemistry was focally positive.

Cytogenetics

BCL2 gene rearrangement and *MYC* gene rearrangement were detected in paraffin-embedded tissues by Break Apart FISH probe. FISH for *IRF4* rearrangement was negative.

Molecular Studies

Clonal rearrangement of the Ig heavy chain (IGH) was detected by PCR and it was the same in both biopsies

Proposed Diagnosis

Lingual biopsy: Follicular Lymphoma with *BCL2* and *MYC* rearrangement.

Submandibular gland biopsy: Follicular Lymphoma with *BCL2* and *MYC* rearrangement.

Interesting Feature(s)

Simultaneous infrequent localizations of extranodal follicular lymphoma in a patient with early stage disease.

Surgical excision was sufficient for the complete resolution of clinical secondary complications to tumors.

As a molecular peculiarity, a positive MYC rearrangement was demonstrated. This has not been followed by recurrence or transformation into diffuse large B-cell lymphoma in the two years of follow-up. The patient has no received QT regimen at any moment.

The added presence of *MYC* rearrangement in follicular lymphoma is exceptional and its prognostic impact in FL is unclear. In such a case, an individual treatment would be required.

EA4HP24-LYWS-38

46-year-old woman with *in situ* B-cell neoplasm with *MYC* rearrangement

Dr. Mariko Yabe

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Case Description

46-year-old woman had an abnormal finding on screening mammography. US-guided needle biopsy of the left breast showed intermediate grade ductal carcinoma *in situ* (DCIS). Based on the diagnosis of DCIS, left breast lumpectomy was performed. Microscopic evaluation of the lumpectomy specimen confirmed the diagnosis of DCIS, and the lesion

showed extension to the cauterized medial surgical margin. The patient subsequently had left breast medial margin re-excision. Left axillary sentinel lymph node excision was performed at the time of re-excision of DCIS.

Biopsy Fixation Details

10% formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

Histologic section shows bisected, single lymph node with focal confined area (one germinal center) demonstrating numerous scattered tingible body macrophages and medium-sized, atypical monomorphic lymphoid cells with finely clumped chromatin and multiple small nucleoli, morphologically similar to systemic high-grade B-cell lymphoma. Brisk mitotic activity was also present.

Immunophenotype

The follicle of interest expresses CD20, CD10, cMYC, LMO2, LEF1 and BCL6. This follicle does not express BCL2, CD3, CD5, TdT, Cyclin D1 or MUM1. CD21 and CD23 show follicular dendritic cell meshwork associated with this abnormal follicle. EBER-ISH was negative. Ki67 proliferation index was >95%.

Cytogenetics

FISH analysis showed *IGH::MYC* fusion in 90% of cells in the area of interest.
There was no evidence of *BCL2* rearrangement or *BCL6* rearrangement.

Molecular Studies

Not performed.

Proposed Diagnosis

in situ B-cell neoplasm with *MYC* rearrangement

Interesting Feature(s)

This is a case of incidental finding of *in situ* B-cell neoplasm with *MYC* rearrangement at the time of sentinel lymph node excision of breast DCIS. *In situ* B-cell neoplasm with *MYC* rearrangement is reported in otherwise healthy individuals (Kumar J. et al. AJSP 2019). After the diagnosis of *in situ* B-cell neoplasm with *MYC* rearrangement, radiographic evaluation was performed to rule out possible systemic involvement. PET-CT showed weak up-take in the left axillary lesion, most likely reactive changes associated with prior surgical procedure (sentinel node resection). To confirm the diagnosis, additional left axillary lymph node resection was performed. These additionally excised lymph nodes showed reactive follicular and paracortical hyperplasia, consistent with reactive changes after the surgical proedure. *In situ* B-cell neoplasm with *MYC* rearrangement was not seen in these lymph nodes. The patient received Tamoxifen and local radiation therapy for DCIS. No therapy was performed for *in situ* B-cell neoplasm with *MYC* rearrangement.

Cases discussed by the panel

EA4HP24-LYWS-6	Primary cutaneous marginal zone lymphoma / lymphoproliferative disorder (heavy chain class-switched form)
EA4HP24-LYWS-24	Indolent T-cell Lymphoma with Unusual Immunophenotype
EA4HP24-LYWS-35	Indolent T Lymphoblastic Proliferation Associated with A Mediastinal Neuroendocrine Carcinoma
EA4HP24-LYWS-50	EBV+ Mucocutaneous Ulcer with Locally Aggressive Course and Mandibular Fracture
EA4HP24-LYWS-60	Indolent T lymphoblastic proliferation in the setting of follicular lymphoma
EA4HP24-LYWS-74	Indolent T-lymphoblastic Proliferation in Acinic Cell Carcinoma
EA4HP24-LYWS-79	NK-cell lymphoproliferative disorder of the gastrointestinal tract, indolent or aggressive?
EA4HP24-LYWS-96	Indolent T cell lymphoproliferative disorder of the gastrointestinal tract: An evolving disease entity
EA4HP24-LYWS-100	Atypical clonal follicular hyperplasia mimicking follicular lymphoma in a patient with autoimmune disease
EA4HP24-LYWS-115	Primary cutaneous marginal zone lymphoproliferative disorder presenting as a preauricular plaque
EA4HP24-LYWS-117	Indolent T lymphoblastic proliferation in tonsilla palatina
EA4HP24-LYWS-165	*Duodenal-type follicular lymphoma in a 36-year-old male*
EA4HP24-LYWS-167	*Indolent CD8-positive T-cell lymphoproliferative disorder of the scalp*
EA4HP24-LYWS-183	Multinodal Indolent T-lymphoblastic proliferation detected by flow cytometry in concurrence with metastatic ovarian carcinoma
EA4HP24-LYWS-190	Pediatric follicular lymphoma with marginal zone differentiation
EA4HP24-LYWS-191	Indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract with an unusual phenotype
EA4HP24-LYWS-192	Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder.
EA4HP24-LYWS-196	Indolent TdT+ T-lymphoblastic proliferation progressed to T lymphoblastic leukemia/lymphoma
EA4HP24-LYWS-211	Diffuse large B cell lymphoma (DLBCL) in a patient with Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract treated with cyclophosphamide and methotrexate
EA4HP24-LYWS-212	An Indolent Peripheral Blood T-cell Clone Associated with Protracted Eosinophilia
EA4HP24-LYWS-215	An atypical thymic hyperplasia
EA4HP24-LYWS-229	Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder

EA4HP24-LYWS-241	An Unusual Case of Primary Marginal Zone Lymphoma of Class-Switched Type, IgG4-Positive, Presenting with Skin and Conjunctival Lesions
EA4HP24-LYWS-250	EBV-associated T-cell Lymphoproliferative Disorder in a Young Adult
EA4HP24-LYWS-253	Indolent T-cell lymphoma /clonal lymphoproliferative disorder of the gastrointestinal tract - a mimic of coeliac disease/ gluten sensitive-enteropathy
EA4HP24-LYWS-256	Indolent Clonal T-cell Lymphoproliferative Disorder of the Gastrointestinal Tract with Clusters of NK-cells.
EA4HP24-LYWS-266	Proliferation of immature TdT+ lymphocytes in an extrathymic location associated with Unicentric Castleman's Disease
EA4HP24-LYWS-276	Indolent T-cell lymphoproliferative disorder clinically presenting as meningitis
EA4HP24-LYWS-287	CD16dim NK-LGLL in a patient with chronic lymphocytosis and a history of mb. Crohn
EA4HP24-LYWS-290	Neoplasms with indolent behaviour/primary cutaneous lymphoproliferative disease
EA4HP24-LYWS-296	Primary cutaneous marginal zone B-cell lymphoma/lymphoproliferative disorder (PCMZL)
EA4HP24-LYWS-293	An indolent EBV-related clonal T-cell proliferation presenting as chronic rhinosinusitis
EA4HP24-LYWS-315	Indolent T-lymphoblastic proliferation associated with low grade follicular dendritic cell sarcoma and Castleman disease
EA4HP24-LYWS-319	Isolated, Centroblast-Rich, BCL2-Negative, Lymphoid Follicle with Follicular Lymphoma-like Ki67 Staining Pattern and *BCL6* Gain associated with Dermatopathic Lymphadenitis: Is it an Intrafollicular Pediatric-Type Follicular Neoplasm?
EA4HP24-LYWS-322	A Rare Case of Duodenal-Type Follicular Lymphoma Presenting as Small Bowel Obstruction
EA4HP24-LYWS-328	CD4/CD8 double negative indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract
EA4HP24-LYWS-337	Indolent CD4+ T-cell lymphoma of the GI tract with nodal and medullary involvement
EA4HP24-LYWS-340	An indolent extranodal NK/T cell lymphoma
EA4HP24-LYWS-349	A Case of Indolent T-Cell Lymphoma of the Gastrointestinal Tract
EA4HP24-LYWS-351	Cutaneous Marginal Zone Lymphoma
EA4HP24-LYWS-358	Isolated indolent mantle cell lymphoma of the stomach
EA4HP24-LYWS-360	Epidermotropic primary cutaneous marginal zone lymphoma
EA4HP24-LYWS-361	A case of nodal T-follicular helper cell lymphoma mimicking Castleman's disease, hyaline vascular type, with a highly indolent behaviour

EA4HP24-LYWS-378	Duodenal-type Follicular Lymphoma – typically an incidental discovery, & indolent....
EA4HP24-LYWS-380	Indolent PTCL NOS with leukemic picture and skin involvement
EA4HP24-LYWS-386	CD123-negative, *BRAF*-negative Hairy Cell Leukemia
EA4HP24-LYWS-373	Indolent Precursor B-cell Expansion in a Reactive Lymph Node: A Sheep in Wolf's Clothing
EA4HP24-LYWS-376	Classifying an epiglotic lymphoid T proliferation
EA4HP24-LYWS-396	Primary duodenal type follicular lymphoma
EA4HP24-LYWS-404	Duodenal-type follicular lymphoma, a classic case that never goes out of style
EA4HP24-LYWS-408	Clonal T-cell lymphoid infiltrate with TFH phenotype
EA4HP24-LYWS-407	Leukemic Non-Nodal Mantle Cell Lymphoma of the Eye with Plasmacytic Differentation.
EA4HP24-LYWS-419	Marked erythrophagocytosis in a patient with primary cold agglutinin disease
EA4HP24-LYWS-420	An isolated pulmonary nodule: a serious illness?
EA4HP24-LYWS-423	Indolent follicular lymphoma of parotid gland in a patient with melanoma and clonal local plasma cell proliferation associated with Talimogene laherparepvec infusion for metastatic melanoma
EA4HP24-LYWS-427	*Paediatric-type follicular lymphoma, case report uncommon*
EA4HP24-LYWS-441	How to classify recurrent indolent EBV positive T cell lymphoma with subcutaneous panniculitis-like T-cell lymphoma features in an adult patient?
EA4HP24-LYWS-449	Indolent leukemic peripheral T-cell lymphoma with involvement of skin, bone marrow and lymph node
EA4HP24-LYWS-454	Indolent T-cell lymphoma of the gastrointestinal tract
EA4HP24-LYWS-460	Monocytoid B-cell non-Hodgkin lymphoma with TFH cell proliferation
EA4HP24-LYWS-462	A case of Duodenal-type follicular lymphoma.
EA4HP24-LYWS-463	Primary cutaneous marginal zone lymphoma
EA4HP24-LYWS-465	Dominant clonal T-cell proliferation with associated clonal B-cell proliferation: is it a composite T & B cell lymphoma?
EA4HP24-LYWS-471	Indolent primary cutaneous lymphoproliferative disorder with overlapping features between primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (LPD) and primary cutaneous marginal zone LPD.

EA4HP24-LYWS-6

Primary cutaneous marginal zone lymphoma / lymphoproliferative disorder (heavy chain class-switched form)

Dr. Joy Staniforth

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Case Description

A female patient in her sixth decade presented with multiple PET-avid subcutaneous tissue masses mainly in the trunk region. No lymphadenopathy, splenomegaly, or other mass lesions were identified. An incisional biopsy was taken from her back.

Biopsy Fixation Details

The sample was fixed in 10% NBF.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Infiltration of the dermis and subcutis by large interconnecting nodules of lymphoid cells comprising monocytoid, lymphoplasmacytoid, and small lymphoid forms. Plasma cells were admixed and surrounded nodule peripheries, predominantly at the superficial aspects of the infiltrate. Epidermis was not included.

Immunophenotype

The infiltrating lymphoid/plasmacytoid cells were B cells expressing CD20, BCL2, and CD21 (the latter weakly at low level). There were underlying loose CD21/CD23+ follicular dendritic cell meshworks and within these were clusters of variably intense positive staining for BCL6. These BCL6+ forms appeared negative for CD10, showed some equivocal weak BCL2 staining, and did not clearly co-localise with MIB1. There was no significant B-cell expression of CD5, CD43, or CD23; forms were negative for CD10 and Cyclin D1. EBER-ISH was negative. Scattered lymphoid cells across a range of sizes showed a blush of lambda, but not kappa light chain ISH staining. The plasma cells were IgA positive and lambda restricted.

There were dense associated small T cells. Small clusters of CD123+ plasmacytoid dendritic cells were also present within nodule peripheries.

Cytogenetics

No BCL2 or BCL6 gene rearrangements detected by FISH.

Molecular Studies

Not performed

Proposed Diagnosis

Primary cutaneous marginal zone lymphoma / lymphoproliferative disorder (heavy chain class-switched form)

Interesting Feature(s)
BCL6 positivity not clearly co-localising with MIB1 or CD10 positivity, possibly representing low-level BCL6 expression in the colonising B cells rather than residual germinal centres.
IgA positivity in plasma cells.
Deep location of the infiltrate.

EA4HP24-LYWS-24

Indolent T-cell Lymphoma with Unusual Immunophenotype

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Case Description
The patient presented as a 67-year-old male with abdominal cramping, changes in bowel habits and weight loss. He underwent endoscopic examination which showed scalloped mucosa of the duodenum and ulceration of the proximal jejunum.
Biopsy Fixation Details
10% buffered formalin.
Frozen Tissue Available
No
Details of Microscopic Findings
A mucosal lymphoid infiltrate is seen on the biopsies of the duodenum and jejunum. Relative lack of epidermotropism and few background eosinophils are appreciated. The lymphocytes are small to intermediate in size with irregular nuclei, a small amount of cytoplasm and indistinct nucleoli.
Immunophenotype
The infiltrating cells are positive for CD3, CD2, PD1 (weak), CD30 (weak), TCR A/B and are negative for CD5, CD7, CD8, TCR G/D, ALK1, CD10, BCL6, CD56, BCL2, TIA1, Granzyme B. CXCL13 shows focal staining. EBV ISH stains very rare small B-cells. Ki-67 shows a low proliferative index (<10%).
Cytogenetics
Not performed.
Molecular Studies
TCR gene rearrangement studies by NGS show a clonal rearrangement pattern for TCRG (two dominant peaks: 66.97% of reads and 23.29% of reads). NGS whole exome studies showed a likely pathogenic variant in FAT1 (p.Gly772Ala, c.2315G>C) at 8.06% VAF. FAT1 is a tumor suppressor gene and variants in this gene have been reported as frequent mutations in peripheral T-cell lymphomas with data suggesting a poor prognostic impact.
Proposed Diagnosis
Indolent T-cell lymphoma of the gastrointestinal tract

Interesting Feature(s)

The T-cells show an immunophenotype that is unusual for this entity, as CD4+ cases have generally been reported to be negative for PD-1 and CD30 has been reported as negative except in transformed cases. Despite the unusual immunophenotype, the clinical and morphologic features as well as the low proliferative rate appear to best fit an indolent T-cell lymphoma of the gastrointestinal tract. A FAT1 variant was detected which is a frequently mutated gene in PTCL, NOS with reported survival implications although it has not been been previously reported in this entity to our knowledge.

EA4HP24-LYWS-35

Indolent T Lymphoblastic Proliferation Associated with A Mediastinal Neuroendocrine Carcinoma

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Case Description

A 48 y/o male with minimal medical history reports worsening facial and bilateral upper extremity swelling for one month. He notes dizziness, feeling pressure in his eyes, occasional cough, throat tightening and change in voice. He was a former smoker who had smoked since he was in his teens. He quitted 15 years ago. CT chest with IV contrast revealed large mediastinal mass measuring 8.0 x 7.8 x8.1cm which compresses and may obstruct superior vena cava. Ultrasound revealed 4 cm lymph nodes in right and left axilla. Mediastinal excisional biopsy was performed.

Biopsy Fixation Details

The tissue was submitted in 10% neutral buffered formalin.

Frozen Tissue Available

Intraoperative consultation was requested and air-dried touch preparation was made. The Diff-Quik stain showed discohesive "lymphoid cells" and flow cytometry study was ordered.

Details of Microscopic Findings

Histology sections show multiple fragments of soft tissue showing diffuse infiltration of intermediate size atypical cells forming clusters and nests with intervening fibrosis, suggestive of neuroendocrine tumor. These tumor cells are intermixed with sparse small mature lymphoid cells. Separately are two fragments of lung parenchyma showing acteletasis. In the narrowed alveolar space, there are scattered small lymphoid cells and focally forming small clusters.

Immunophenotype

Immunohistochemical stains showed the tumor cells are diffusely and strongly positive for cytokeratin CAM 5.2 and PAX8, focal positive for CD56 and NSE, and focal weakly positive for synaptophysin. They are negative for chromogranin, TTF-1 and CD10.

The small lymphoid cells are positive for CD3, TDT, and c-MYC. Ki-67 stain shows similar pattern as CD3. TTF-1 outlines the alveolar lining, consistent with lung parenchyma.

Cytogenetics

Not available

Molecular Studies

T cell receptor gene rearrangement study was performed but failed to detect a clonal peak.

Proposed Diagnosis

Indolent T Lymphoblastic Proliferation Associated with A Mediastinal Neuroendocrine Carcinoma

Interesting Feature(s)

Indolent T lymphoblastic proliferation had been described. An association with Castleman disease, Castleman-like features, dendritic cell proliferations in general is well-known. In addition, there is high frequency of concurrence with hepatocellular carcinoma and autoimmune diseases. This is the first case of indolent T lymphoblastic proliferation associated with neuroendocrine carcinoma. In addition, most of the cases, the T lymphoblasts reported co-express of CD4 and CD8. In our case, the flow cytometry analysis showed two different component of immature T lymphoblasts, one population is CD3 positive, similar to the cortical thymic T cells which include various amount of CD4 and CD8 double positive T cells and either CD4 and CD8 single positive T cells. The second population is CD3 negative T cells double negative which express CD5 (dim), bright CD7, consistent with the most immature T lymphoblasts.

The relation between the neuroendocrine tumor and the T lymphoblastic proliferation is unknown. The presence of seeming normal thymocytes admixed with the immature T lymphoblasts, which can only be separated by flow cytometry analysis, raises the possibility that the T lymphoblastic proliferation derived from the co-existing thymocytes the microenvironment of neuroendocrine carcinoma with left shift in T cell differentiation.

Indolent T lymphoblastic proliferation is likely under-reported with minimal cytologic atypical appearing as tumors associated lymphocytes. The patient was treated for neuroendocrine carcinoma with Carbo+ etoposide + Radiation therapy without leukemia.

EA4HP24-LYWS-50

EBV+ Mucocutaneous Ulcer with Locally Aggressive Course and Mandibular Fracture

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Case Description

A 49-year-old man originally presented with EBV negative diffuse large B cell lymphoma involving the tongue and posterior nasopharynx with remission after chemotherapy. Immunodeficiency investigations show low IgG (522mg/dL) and low IgM (<25mg/dL). He was diagnosed with combined variable immunodeficiency (CVID) and treated with immunoglobulin replacement. Four years later, he re-presented with a new PET-avid ulcerating lesion on the left tonsil and soft palate. He received rituximab initially, without remission, before undergoing resection four months later. Two months post-resection, the ulcerative mass regrew. The patient then underwent external beam radiation therapy. Within four months, the area showed new FDG uptake and after eight months, a repeat biopsy was performed. The patient was then treated with Brentuximab. Despite Brentuximab treatment, PET/CT remained suspicious for persistent disease. After three months, he underwent bone biopsy which showed osteomyelitis with actinomyces species present. A month later, he presented with a non-traumatic fracture of the left body of the mandible with osteolytic/necrosing bone extending to the ramus. His jaw was stabilized for three months before mandibulectomy and debridement. Culture of the fracture site grew Actinomyces. The patient was then transitioned to pembrolizumab.

Biopsy Fixation Details

Soft tissue resections / biopsies were fixed with formalin or B+ fixative. Bone resection was formalin-fixed and decalcified with RapidCal Immuno.

Frozen Tissue Available

No

Details of Microscopic Findings

Initial DLBCL histology is not available. All soft tissue resections showed similar necrotic mucosal ulcer beds with a well-delineated edge of viable inflammatory cells. At high power, the inflammatory infiltrate included admixed larger lymphocytes in a background of small lymphocytes and histiocytes without neutrophilia. The mandibular resection showed osteomyelitis.

Immunophenotype

The ulcer edge was defined by a prominent rim of small CD3+ T cells with intermixed larger lymphocytes. Initially, the larger lymphocytes were positive for Pax5, CD20, CD30 (weak), CD15, MUM-1, BCL-6 and EBER but lost staining for Pax5 and CD20 in later specimens. The

large lymphocytes showed moderate proliferation (~60% Ki-67). In situ hybridization for EBER highlighted the large lymphocytes.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

EBV+ mucocutaneous ulcer with locally aggressive features

Interesting Feature(s)

EBV+ mucocutaneous ulcer (MCU) is typically considered indolent and can regress spontaneously or with immunosuppressant withdrawal. In contrast, this case was locally aggressive, recurred after multiple lines of therapy and was associated with a mandibular fracture. Although it is unclear if the mandible fracture was directly related to the MCU, indirectly related via local immunomodulation or iatrogenic secondary to radiation-induced osteonecrosis, it indicates that serious sequelae can occur in MCU. This possibility is further supported by a growing number of reported cases of locally aggressive disease. This locally aggressive EBV+ MCU arising in close proximity to a prior EBV negative DLBCL also raises the possibility of predisposing local immunomodulatory or stromal change. In addition, this aggressive occurrence of MCU in a patient with CVID also suggests that baseline immunodeficiency may contribute to disease course. This case of MCU supports the recognition that a subset of MCU cases may be locally aggressive. Further study is needed to better characterize these cases and optimize management.

EA4HP24-LYWS-60

Indolent T lymphoblastic proliferation in the setting of follicular lymphoma

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Case Description

The patient was a 46-year-old male who initially presented with right iliac lymphadenopathy in 10/2016. Core needle biopsy of the right groin lymph node showed follicular lymphoma, grade 1-2, predominantly diffuse pattern. The patient completed 6 cycles of bendamustine and rituximab in 3/2017. PET scan in 05/2017 showed evidence of disease progression with increase in in the metabolic activity and volume in right pelvis. Core needle biopsy of the right pelvic mass showed follicular lymphoma, grade 2, with atypical lymphoid follicles with increased proliferation index and a minor immature T-cell population, suggestive of indolent T lymphoblastic proliferation. No bone marrow

involvement was identified. The patient then completed 2 cycles RICE chemotherapy in 05/2017 and 06/2017.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

The lymphoma shows a predominantly diffuse growth pattern with growth between and around a few widely-spaced atypical lymphoid follicles. The lymphoma cells consist predominantly of small to medium-sized cleaved cells. In addition, a few widely-spaced and ill-defined lymphoid follicles are also present. These consist of a mixed population of medium-sized cleaved cells with finely granular chromatin and inconspicuous nucleoli and interspersed large lymphocytes with small nucleoli. Scattered apoptotic cells and tingible body macrophages are noted.

Immunophenotype

By immunohistochemistry, the diffuse component of the lymphoma expresses CD20, CD23, BCL2, and BCL6, with Ki67 proliferation index about 10-15%. These lymphoma cells are negative for CD10. The lymphocytes in the atypical follicles express CD20, weak/partial CD10 (subset), and BCL6. Unlike the diffuse/ interfollicular component, the atypical follicles do not show significant expression of CD23 or BCL2. Also, they show an elevated Ki67 proliferation index of about 30-50%, without obvious polarization. In addition, multifocal, scattered small TdT+ cells are present, occasionally surrounding the atypical follicles. Flow cytometry confirms a monoclonal B cell population (42% of total cells) expressing CD19, CD20 (bright), CD22, CD23 (variable), sIg kappa, FMC7, and CD38; and negative for CD5, CD10, CD11c, CD43, sIg lambda, and other T cell and myeloid markers. Finally, a minor immature T-cell population is noted by flow cytometry (8.8% of total cells), expressing cytoplasmic CD3, variable surface CD3, CD2, CD5, with co-expression of CD4 and CD8, and expression of nuclear TdT.

Cytogenetics

FISH negative for BCL2/IGH t(14;18) and BCL6 translocations.

Molecular Studies

N/A

Proposed Diagnosis

- Follicular lymphoma, grade 2 of 3, with predominantly diffuse pattern.
- Atypical lymphoid follicles with increased proliferation index.
- Minor immature T-cell population, suggestive of indolent T lymphoblastic proliferation.

Interesting Feature(s)

Here we report a case of follicular lymphoma with concurrent indolent T lymphoblastic proliferation(iTLBP). The proliferative T lymphoblastic cells are noted by flow cytometry and express cytoplasmic and surface CD3, CD2, CD5, TdT with coexpression of CD4 and CD8. On histology, multifocal, scattered small TdT+ cells without overt morphological atypia are also noted. These features fit the major criteria for iTLBP.

EA4HP24-LYWS-74

Indolent T-lymphoblastic Proliferation in Acinic Cell Carcinoma

Dr. Chee Leong Cheng

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Case Description

40 years old, Male, Asian. No past medical history of note.

He presented with left parotid tumour and imaging revealed left parotid deep lobe tumour.

There are no other constitutional symptoms of note. There are no other abnormal haematological features of note.

A left parotidectomy was performed. We received a parotid gland measuring 4 x 3 x 3.5cm, containing a tan-brown fleshy tumour measuring 3.5 x 2.5 x 3.5cm abutting the external surface.

Follow up unremarkable (including 5 years post diagnosis).

Biopsy Fixation Details

Received left parotidectomy specimen fixed in 10% neutral buffered formalin.

Frozen Tissue Available

Nil

Details of Microscopic Findings

Parotid tumour is composed of nests and interconnecting islands of epithelial cells admixed with a dense lymphoid infiltrate.

The epithelial nests and islands show small acinar/ductular spaces, and the constituent cells exhibit small round-to-ovoid nuclei with occasionally small nucleoli and eosinophilic granular/vacuolated cytoplasm, without significant nuclear pleomorphism or necrosis present. Special histochemical stains reveal the presence of PAS positive, diastase-resistant zymogen granules within the cytoplasm of these epithelial tumour cells, which are also diffusely immunoreactive for DOG1 and SOX10.

The background lymphoid component shows a dense infiltrate of predominantly small lymphocytes with a few scattered small germinal centres, the latter preferably seen in the more peripheral aspect of the tumour. The lymphoid cells are predominantly small lymphocytes with bland appearance.

Immunophenotype

Immunohistochemistry reveals a generally compartmentalised lymphoid architecture (within the limits of some disruption by epithelial tumour islands), with CD20(+)/PAX5(+) B-follicles that are mostly primary follicles comprising IgD(+)/bcl-2(+)/CD23-weak naïve B-cells, accompanied by a few small CD10(+)/bcl-6(+)/bcl-2-negative/Ki-67-high and polarised, reactive germinal centres, based on circumscribed, CD21/CD23-immunoreactive follicular dendritic meshworks. CD3 and CD5 immunostaining highlights interfollicular T-cells, most of which are small and without any significant cytologic atypia. However, there are also

patchy aggregates of predominantly small TdT(+)/CD3(+)/CD5(+)/TCR-beta-F1-negative T-lymphoblasts which are also CD10(+), CD1a(+), CD99-intense (contrasting against background CD99-weak, mature T-lymphocytes) and Ki-67-high, many of which are perithelial in location, although these T-lymphoblasts do not form sheets effacing the epithelial components of the tumour.

Cytogenetics

Nil

Molecular Studies

Nil

Proposed Diagnosis

Indolent T-lymphoblastic Proliferation in Acinic Cell Carcinoma

Interesting Feature(s)

Relatively florid proliferation of T-lymphoblasts, raising concern of T-lymphoblastic leukaemia/lymphoma.

However, the cytological features of these T-lymphoblasts are bland and lack sheet-like morphology of an overt lymphoblastic neoplasm.

Follow up is unremarkable, with no features of T-lymphoblastic leukaemia/lymphoma.

EA4HP24-LYWS-79

NK-cell lymphoproliferative disorder of the gastrointestinal tract, indolent or aggressive?

Dr. Min Shi, Dr. Andrew L. Feldman, Dr. Rong He, Dr. Ji Yuan

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Case Description

A 35-year-old female presented with abdominal pain, nausea, vomiting, diarrhea, and a 100lb weight loss over one year. She denied fever or night sweats. Her multiple family members have Crohn's disease. An CT scan showed thickening of the small bowel wall, a possible fistula, and lymphadenopathy with the largest one measuring 2.2 cm. GI endoscopy revealed small ulcers and a large 8 cm circumferential ulcer in the jejunum, leading to luminal narrowing, which was biopsied (specimen 1). The diagnosis of NK-cell lymphoproliferative disorder (NKLPD) was rendered. However, given her aggressive clinical presentation, NK-cell lymphoma was clinically favored. Before chemotherapy, a small bowel resection was performed to avoid perforation (specimen 2). Surprisingly, the resection specimen showed features of inflammatory bowel disease with focal minimal NKLPD. The patient has been doing well without chemotherapy. A repeat CT scan did not show recurrent inflammatory disease or lymphoma.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Specimen 1: Fragments of ulcerated small bowel mucosa revealed a dense lymphoid infiltrate in the lamina propria, consisting of small to intermediate-sized cells with irregular nuclear contour, small nucleoli and abundant cytoplasm. Lymphoepithelial lesions are evident focally.

Specimen 2: Resection specimen showed superficial ulceration, transmural inflammation with lymphoid aggregates and fibrosis, and possible fistula formation.

Immunophenotype

Specimen 1: Lymphocytes were positive for CD2, CD3 (dim), CD8 (dim) and CD56, and negative for CD4, CD5, CD20, CD30, granzyme B, TCR-βF1, TCR-delta and EBER. The expression of CD7 and TIA1 was maintained on the lymphocytes within lymphoepithelial lesions but was absent on those of lamina propria.

Specimen 2: Transmural inflammation comprised reactive CD3+ T cells with intact T-cell antigen expression and a normal CD4:CD8 ratio. CD20 highlighted reactive follicles. Focally, there were CD2+, CD3 (dim)+, CD7-, CD8 (dim)+, CD56+ NK cells present superficially along the ulcerated mucosa.

Cytogenetics

NA

Molecular Studies

Specimen 1 showed no clonal *T-cell receptor* gene rearrangement and revealed pathogenic mutations in

JAK3: Chr19(GRCh37):g.17949108C>T;NM_000215.3(*JAK3*):c.1533G>A;p.Met511Ile(6%) C hr19(GRCh37):g.17948009G>A; NM_000215.3(*JAK3*):c.1715C>T; p.Ala572Val (8%)

Proposed Diagnosis

Indolent NK-cell lymphoproliferative disorder (I-NKLPD) of the gastrointestinal tract in a background of Crohn's disease

Interesting Feature(s)

Significant overlaps in clinical, morphological, immunophenotypical, and genetic characteristics between I-NKLPD and EBV-negative extranodal NK-cell lymphoma can lead to diagnostic challenges. Patients with I-NKLPD typically experience mild symptoms along with superficial ulcers or polyps in the GI tract. However, when I-NKLPD is complicated by Crohn's disease, patients may exhibit aggressive clinical presentations and large ulcerative lesions, as observed in this patient. Furthermore, I-NKLPD may display cytologic atypia, lymphoepithelial lesions, antigen loss, and genetic mutations. Therefore, it is crucial to include I-NKLPD in the differential diagnosis for small and superficial GI biopsies to avoid overdiagnosis.

The activation of the JAK/STAT pathway has been implicated in the pathogenesis of both I-NKLPD and Crohn's disease. While recurrent somatic *JAK3* mutations are observed in I-NKLPD, there have been no reported cases of *JAK3* mutations in Crohn's disease. The relationship between the *JAK3*-mutated I-NKLPD and Crohn's disease remains uncertain.

EA4HP24-LYWS-96

Indolent T cell lymphoproliferative disorder of the gastrointestinal tract: An evolving disease entity

Dr. Claire Abou-Seif[1,2], Prof. Beena Kumar[1,2], Dr. Michael Low[1,3], Dr. Luke Wang[1]

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Case Description

A 37-year-old female born in Afghanistan presented to our hospital with a 3-week history of post-prandial abdominal pain associated with nausea, vomiting, diarrhoea and a weight loss of 10kg. Her history was significant for endometriosis and previously treated tuberculosis. Initial work up revealed a normal full blood examination, liver function tests, inflammatory markers and LDH. A CT abdomen, pelvis showed diffuse mild thickening of the small bowel, numerous mildly enlarged mesenteric lymph nodes (largest up to 1.4cm) and splenomegaly (16.1cm craniocaudal height) which was again seen on a follow up MRI enterogram for work-up of chronic diarrhoea. Her faecal PCR was unremarkable, and no ova, cysts or parasites were detected. Coeliac serology was negative.

Further work-up with endoscopy revealed macroscopically patchy friable mucosa in the first portion of the duodenum and normal colonoscopy. A biopsy was performed. A positron emission tomography demonstrated persisting mesenteric lymphadenopathy but with mild avidity (SUV ≤2). A mesenteric node biopsy was later completed and a bone marrow biopsy was also done.

Biopsy Fixation Details

The specimen was fixed in 10% formalin for 14 hours prior to processing according to a specific protocol (see Slides)

Frozen Tissue Available

N/A

Details of Microscopic Findings

Biopsies taken of duodenal and terminal ileal mucosa demonstrated significant villous blunting with sparse intraepithelial lymphocytes. Within the lamina propria there was a dense infiltrate of small lymphocytes showing mild atypia with mild nuclear variability and nuclear membrane irregularities with small numbers of admixed plasma cells and eosinophils. No large atypical or Reed-Sternberg like cells were found. No viral inclusions were seen.

Immunophenotype

Immunohistochemistry showed strong positive staining within the lymphoid population for CD2, CD3 and CD5 with downregulation of CD7. There was also strong diffuse expression for CD4 with only rare CD8 positive cells noted. CD20 showed incomplete membranous and granular cytoplasmic staining interpreted as aberrant expression. Immunostaining for

PAX5, CD79a and Mum-1 showed small numbers of B cells only. Staining for CD56 and EBER-ISH were negative. The Ki67 index was between 5 to 10%.

Cytogenetics

Not performed

Molecular Studies

Not performed

Proposed Diagnosis

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

Interesting Feature(s)

Aberrant CD20 expression – significance uncertain

Patient was started on corticosteroids, later transitioned to cyclosporin to good effect

EA4HP24-LYWS-100

Atypical clonal follicular hyperplasia mimicking follicular lymphoma in a patient with autoimmune disease

Prof. Tanuja Shet, Dr. Uma Sakhdeo

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Case Description

45-year-old lady presented in Jan 2023 with neck nodes last 10 years. There was recent increase in size of neck node and new onset left neck node

O/E Cervical node 3X3 cm with skin thickening with erythema in nape of neck and right supra mammary region

PET CT: 16/2/23: Hypermetabolic bilateral cervical adenopathy (level III and V on left). Hypermetabolic subcutaneous nodule at the nape of the neck s/o lymphomatous involvement

No evidence of metabolically active disease noted elsewhere in the scan.

•Neck node biopsy was done and During subsequent follow up patient gave history of skin lesion excision done in June 2022 and that is the second biopsy submitted

Initial diagnosis Called as atypical B lymphoid proliferation favor low grade Follicular lymphoma with skin involvement

However Clinically patient had nodes for long time and also joint pains and impression was of autoimmune disease, On further testing ANA/ dsDNA was positive – but as patient was not clinically incapacitated by disease Patient was kept on observation and within a month all lesions regressed!

•12 months since last follow up no relapse and PET scan is negative

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Lymph node: Node shows partial loss of architecture with a repertoire of changes in follicles, Some follicles were reactive while some showed centrocyte predominant population of cells suggestive for follicular lymphoma. Few follicles showed larger cells suspicious for transformation

SKin biopsy - Histology revealed deep dermis showing follicles composed of centrocyte and Centroblast infiltrating into the deep subcutaneous tissue but lesion as circumscribed

Immunophenotype

Lymph node

•There were clearly some follicles that were suspicious for follicular lymphoma which were CD10 negative, bcl2 positive, BCl6/LMO2 positive but with no interfollicular spill.

•The larger cells were CD20 and CD30 positive but CD15/GATA3/ EBERISH were negative

•CD21 revealed a intact dendritic network within follicles

•MUM1 revealed few plasma cells in interfollicular area but was negative in follicles

•MIB1 showed reactive and neoplastic type of pattern

Summary of flow cytometry done on neck node

CD45 Moderate, CD20 bright, CD19 Mod –dim, CD38 moderate, CD180 moderate IgM moderate, Lambda negative, Kappa positive

CD305LAIR1, CD200, Cd10, Cd25, CD148 negative, CD4, CD8, Cd5, CD7 negative CD11c, CD15 negative, Ki67 3.9%

Skin Biopsy: •Follicles were positive for LMO2, bcl6, bcl2 with a uniformly distributed (unlike normal germinal centre) MIB1 of 20%, CD10 was negative

•Skin lesion diagnosis Follicular lymphoma involving skin Unlikely to be primary follicular cutaneous lymphoma there were follicles which were bcl2 positive)

Cytogenetics

•Bcl2 FISH was performed using **Zyto*Light*® SPEC BCL2 Dual Color Break Apart Probe.** It revealed that most follicles had no break apart signals but in four to five follicles bcl2 FISH showed 10% nuclei with break apart signals indicating bcl2 rearrangement

Molecular Studies

Clonality on block will be done.

Proposed Diagnosis

Atypical clonal follicular hyperplasia mimicking follicular lymphoma in a patient with autoimmune disease

Interesting Feature(s)

•We have not come across any description of such a case in literature

•The histology mimicked follicular lymphoma but clearly this was a lymph node manifestation of autoimmune disease

•Some clues to avoid misdiagnosis in retrospect -The lesion lacked clear cut diagnostic features of follicular lymphoma with interfollicular spill, bcl2 was patchy positive.

EA4HP24-LYWS-115

Primary cutaneous marginal zone lymphoproliferative disorder presenting as a preauricular plaque

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Case Description

A 54-year-old woman with medical history of autoimmune hepatitis, consulted in 2019 for a slowly-growing preauricular erythematous plaque, without pruritus or pain. A punch biopsy was performed.

After the diagnosis, the patient was treated with intralesional Rituximab and radiation therapy. Local and preauricular contralateral relapses were diagnosed in 2020, 2021 and 2022, and were treated with systemic Rituximab. In 2023, the patient noticed progressive swelling of the parotid gland. The excisional biopsy showed glandular and regional lymph node spread of the disorder. The patient is currently under treatment with Zanubrutinib.

Biopsy Fixation Details

10% buffered formalin fixed and paraffin-embedded.

Frozen Tissue Available

Not-available.

Details of Microscopic Findings

The cutaneous biopsy showed a dense multinodular infiltrate that extended to the subcutis, composed of small lymphocytes with monocytoid morphology, occasional plasma cells and lymphoid follicles with reactive germinal centers.Multiple subsequent cutaneous biopsies showed similar histologic pattern. Parotid gland and cervical lymph node biopsies showed partial infiltration by monocytoid lymphocytes without significant lymphoepithelial lesion.

Immunophenotype

Neoplastic cells in the initial and subsequent biopsies expressed B-cell markers (CD20, CD79a) as well as BCL2, but were negative for CD10 and BCL6. The reactive germinal centers contained a network of dendric cells (CD21 and CD23 positive). IgM was positive in the majority of the lymphoid population. In situ hybridization for light chains showed no restriction. Proliferation rate (ki67) was 80% in the germinal centres, and less than 10% in the interfollicular areas.

Cytogenetics

Not done.

Molecular Studies

PCR: same clonal rearrangement ofIgH (FR1, FR2 and FR3 regions, BIOMED protocol) in all biopsies.

Proposed Diagnosis

Primary cutaneous marginal zone lymphoproliferative disorder (PCMZLPD)

Interesting Feature(s)

IgM-positive PCMZLPD are less frequent than their class-switched counterparts, and present with subcutaneous and extracutaneous involvement more often. The present case spread to subcutis, parotid gland and regional lymph nodes, maintaining its low-grade morphology and low proliferation index.

EA4HP24-LYWS-117

Indolent T lymphoblastic proliferation in tonsilla palatina

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Case Description

35-year-old male patient with history of Langerhans cell histiocytosis (LCH) at left humerus in 2021, treated with radiotherapy following excision. During follow up PET-CT imaging revealed high FDG uptake at bilateral tonsilla palatinas (SUVmax: 11,9). Bilateral tonsillectomy was performed to rule out LCH recurrance.

Biopsy Fixation Details

Tonsillectomy specimens was fixed in 4% formaline.

Frozen Tissue Available

None.

Details of Microscopic Findings

Reactive follicular hyperplasia was seen in both tonsils. No morphologic evidence of LCH was detected. In case of a subtle infiltration immunohistochemisrty was performed.

Immunophenotype

Agregate of S100 (-) , CD1a(+) cells was discovered. Due to the CD1a positivity immunohistochemical work up expanded. CD1a positive cells found to be positive for TdT and CD3; negative for CD79a.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Indolent T lymphoblastic proliferation

Interesting Feature(s)

Incidental discovery of indolent T lymphoblastic proliferation at a patient with previous history of LCH and RT.

EA4HP24-LYWS-165

Duodenal-type follicular lymphoma in a 36-year-old male

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Case Description

The patient is a 36-year-old male who presented with worsening abdominal pain and blood in his stool. He underwent and esophagogastroduodenoscopy (EGD) and colonoscopy. The colonoscopy showed a 4mm rectal polyp and a 6mm terminal ileum ulcer, but otherwise negative. The EGD showed a normal esophagus and normal 1st and 2nd parts of the duodenum, but also showed diffuse moderate inflammation of the stomach. Biopsies were taken and a duodenal biopsy showed duodenal type follicular lymphoma. He has been on observation since the diagnosis. Five years later, the patient has been doing well without significant gastrointestinal symptoms. Repeat EGD and colonoscopy showed nodularity in the duodenum and terminal ileum. Duodenal and terminal ileum biopsies showed persistent duodenal type follicular lymphoma. Since he remains asymptomatic, he will continue with observation with regular follow-up every 12 months.

Biopsy Fixation Details

10% formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

Both the duodenal and terminal ileum biopsies showed multiple nodular proliferation of atypical lymphoid follicles in the small intestinal mucosa. These atypical lymphoid follicles were composed of small lymphoid cells with coarse chromatin, irregular nuclei and scant cytoplasm. Centroblasts were rarely seen.

Immunophenotype

The atypical lymphoid follicles were positive for CD20, CD10, BCL-6 and BCL2. CD23 highlighted the follicular dendritic meshworks. CD3 and CD5 highlighted the background T-cells. The Ki-67 proliferation index was approximately 5%.

Cytogenetics

N/A

Molecular Studies

N/A

Proposed Diagnosis

Duodenal-type follicular lymphoma.

Interesting Feature(s)

This is a classic case of duodenal type follicular lymphoma. The follicular lymphoma is confined to the duodenal and terminal ileum mucosa without extra GI involvement. The

lymphoma cells showed typical phenotype of FL with expression of germinal center markers CD10 and BCL2, and BCL2. The clinical course is very indolent and the patient required no treatment.

EA4HP24-LYWS-167

Indolent CD8-positive T-cell lymphoproliferative disorder of the scalp

Richard Shao[1], **Dr. Ling Zhang**[2]

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Case Description

The patient is a 74-year-old male with history of chronic myeloid leukemia, chronic phase, status post treatment with Gleevec and Bosutinib with good response, and multiple squamous cell cancers of the scalp. He noticed progressively growing lesion of the right scalp, which led to the skin biopsy, which resulted in a diagnosis of CD8-positive clonal T-cell lymphoproliferation. The patient has been on observation and has no new skin lesion development after 5 years.

Biopsy Fixation Details

10% formalin fixation

Frozen Tissue Available

N/A

Details of Microscopic Findings

The right scalp skin biopsy showed a diffuse infiltrate in the subcutaneous by sheets of small atypical lymphoid cells with irregular to angulated nuclei, coarse chromatin and scant to moderate cytoplasm. Large lymphoid cells were rarely seen.

Immunophenotype

CD3 highlighted sheets of T-cells. The T-cells were positive for CD2, CD5, CD8 and TCR bF1, and negative for CD4, CD56, and CD57, and showed loss of CD7. They showed a low proliferation rate by Ki-67 (~10%). EBER is negative.

Cytogenetics

N/A

Molecular Studies

PCR demonstrated a clonal TCR-beta and TCR-gamma gene rearrangements.

Proposed Diagnosis

Indolent CD8-positive T-cell lymphoproliferative disorder.

Interesting Feature(s)

This an unusual case of indolent CD8-positive T-cell lymphoproliferative disorder (LPD) presented in the scalp. Morphologically and phenotypically, it resembles the primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder/primary cutaneous acral

CD8 positive T-cell lymphoma that usually occurs in the ears, nose, hands and feet. Rather than in the dermis, this case showed location primarily in the subcutaneous tissue. The clinical course supports the benign nature of the disease. This case indicates that primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder can occur in unusual locations and in subcutaneous tissue.

EA4HP24-LYWS-183

Multinodal Indolent T-lymphoblastic proliferation detected by flow cytometry in concurrence with metastatic ovarian carcinoma

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Case Description

Our patient is a 53-year-old female diagnosed with metastatic ovarian high-grade serous adenocarcinoma who received Neoadjuvant chemotherapy, targeted therapy (Bevacizumab) and debulking surgery (total hysterectomy with bilateral salpingo-oophorectomy). Follow-up PET/CT scan showed a malignant process involving lymph nodes (LNs) above and below the diaphragm, spleen, and mesenteric nodules, suggestive of lymphoma rather than metastasis. LNs biopsies were performed and sent for flow cytometry (FCM) testing.

Biopsy Fixation Details

formalin-fixed, paraffin-embed-ded

Frozen Tissue Available

N/A

Details of Microscopic Findings

The lymph nodes (LNs) (both axillary and inguinal) were almost totally occupied (>90% of the total tissue examined) by metastatic high-grade carcinoma of ovarian origin.

LN cytospin preparation wasinfiltrated with clusters of non-hematopoietic cells within a background of immature-looking lymphoid cells with less condensed nuclear chromatin. BM is negative.

Immunophenotype

LNs biopsies were sent for flow cytometry (FCM) and detected abnormal population of precursor T-cells ~ 11%, expressing CD45 (moderate), cytoplasmic CD3, CD2, CD5 (dim), CD7 (dim), co-expressing CD4, CD8 (dim), CD1a and TdT (dim) with partial expression of CD10 & TCR alpha/beta. This abnormal population is negative for CD34. In addition, >90% of the

submitted tissue was infiltrated by ovarian carcinoma, highlighted by AE1/3, WT1, CK7, PAX-8, p53 and ER. No overt abnormal population of lymphoid cells seen on routine stains. Based on the result of FCM, the lymphoid component was reassessed and showed a population of cells (<10%) of the LN that expresses CD3, CD5, CD10 and TdT.

Cytogenetics

Not done

Molecular Studies

Molecular Testing for *TCR gene* rearrangements was performed on LN by PCR analysis and showed

Gaussian distributions consistent with polyclonal T-cells and absence of any clonal population

Proposed Diagnosis

Indolent T-lymphoblastic proliferation (iT-LBP)

Interesting Feature(s)

iT-LBP has emerged as a distinct pathologic entity and its recognition has increased after being recently listed in the WHO classification of hematopoietic neoplasms 5thedition under the umbrella of tumor-like lesions with T-cell predominance. iT-LBP is a very rare entity with a total number of reported cases amounting to a total of 54 cases and the case below is the first report from Qatar. As iT-LBPs share immunophenotypic similarities with T-lymphoblastic lymphoma (its aggressive mimic); hence the importance of its recognition and differentiation. The subtle involvement of LNs by TdT-positive precursor T -cells, low percentage of precursor T-cells detected by FCM, concurrent LN involvement by carcinoma together with the indolent clinical course and negative bone marrow all raised the suspicion for iT-LBP, which later confirmed by absence of T-cell clonality. Molecular studies play a pivotal role in differentiating this entity from T-ALL/LBLL and similar to our case, all iT-LBP cases reported in the literature showed absence of T-cell clonality. One of the major criteria for diagnosis of iT-LBP is confirmation of indolence nature of the disease which needs more than 6 months follow-up without significant progression in the absence of treatment. Reporting cases of iT-LBPs is very crucial to increase the awareness of this entity which could be easily mis-diagnosed as T-ALL/T-LBLL with the risk of exposure to unneeded chemotherapy.

EA4HP24-LYWS-190

Pediatric follicular lymphoma with marginal zone differentiation

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Case Description

A 15-year-old female, presented with an enlarged post-auricular lymph node/mass of 2 months duration. She just completed a 10-day course of clindamycin with no improvement. She had no significant symptoms including fevers, cough, night sweats and weight loss. Laboratory testing revealed normal complete blood counts with no lymphocytosis, elevated LDH and fibrinogen levels. Imaging studies showed no other lymphadenopathy or organomegaly. The lymph node/neck mass was completely excised and submitted for evaluation. The patient did not receive further treatment and has been in complete remission (54 months later) as of January 2024.

Biopsy Fixation Details

Lymph node/neck mass. 10% neutral buffered formalin fixed, paraffin embedded sections.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Histologic sections of the biopsy show an atypical lymphoid infiltrate involving entrapped salivary glandular elements with extension into the adjacent soft tissue. The infiltrate shows a vaguely follicular/serpiginous growth pattern, lack polarization and have attenuated mantle zones. The infiltrate is composed of predominantly medium sized lymphoid cells with admixed tingible body macrophages. The interfollicular areas have a more monocytoid appearance.

Immunophenotype

The immunohistochemical staining of the abnormal lymphoid infiltrate demonstrated expression of CD20, CD10 and BCL6 and are kappa light chain restricted by kappa and lambda stains. The atypical cells also show expression of MUM1. The atypical B cells were negative for BCL2, CD5, CD23, CMYC and cyclin D1. Ki-67 showed a high proliferative rate (>70%). EBER-ISH was negative. Flow cytometry analysis detected abnormal B cells that were positive for CD19, CD20 and CD10 with lack of CD5, CD43 and CD23.

Cytogenetics

The chromosomal microarray analysis detected a loss of chromosome X. Flourescence-in-situ hydridization studies for IRF4, BCL2, BCL6 and MYC gene rearrangements were all negative.

Molecular Studies

Clonality studies were positive for a clonal immunoglobulin heavy chain gene rearrangement.

Proposed Diagnosis

Pediatric type follicular lymphoma with marginal zone differentiation favored

Interesting Feature(s)

- The biopsy shows many features of a pediatric type follicular lymphoma including presentation of a solitary lesion in the head and neck region with expression of CD10 and BCL6 and weak to negative BCL2 expression.
- There is a MUM1 positive component which in the absence of IRF4 gene rearrangement is suggestive of a marginal zone differentiation.
- The features raised the consideration of pediatric nodal marginal zone lymphoma but the lack of progressive transformation of germinal centers (PTGC) and germinal center marker expression goes against this.

- The absence of IRF4 gene rearrangement excluded a large B cell lymphoma with rearranged IRF4.
- The infiltrate showed extension into the adjacent soft tissue but recurrence did not occur confirming the indolent nature of the lymphoproliferative process.
- The features show overlapping features of both pediatric follicular lymphoma and pediatric nodal marginal zone lymphoma.
- The overall process may represent a spectrum between the two entities.

EA4HP24-LYWS-191

Indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract with an unusual phenotype

Dr. Margaret Moore, **Dr. Ifeyinwa Obiorah**

University of Virginia Hospital, Pathology/Hematopathology, Charlottesville, USA

Case Description

The patient is a 37-year-old female with a history of inflammatory bowel disease and autoimmune hepatitis since 12 years of age. She underwent a living donor liver transplant, including Roux-eny hepatojejunostomy, in 2017. Routine surveillance colonoscopy in 2021 showed active colitis but a terminal ileum biopsy was reported to show no pathologic abnormality. More recently in January 2023, the patient developed recurrent episode of nausea, vomiting associated with abdominal pain occasionally requiring ER visits for pain control. She denies any significant fatigue, fever, chills, unintentional weight loss, itching or night sweats. MRI of the abdomen showed prominence of the afferent jejunal loops, with mild wall thickening in the jejunum and ileum. Another biopsy of the jejunum was performed in August 2023, which was initially thought to be unremarkable by the surgical pathology colleagues. Further review by hematopathology demonstrated an atypical T cell proliferation that was negative for both CD4 and CD8. No further treatment was performed and patient is alive and well. The patient is currently managed with active surveillance with serial imaging and endoscopy with biopsy if any change is noticed.

Biopsy Fixation Details

Jejunum. 10% neutral buffered formalin fixed, paraffin embedded sections

Frozen Tissue Available

None

Details of Microscopic Findings

Histologic sections of the biopsy show a lymphoid infiltrate involving lamina propria with extension into submucosa. The infiltrate is composed of mostly small lymphoid cells with no significant intraepithelial lesions. Definitive features of chronic mucosal injury are not identified. Similar lymphoid proliferations were observed in the other jejunum biopsy and ileum.

Immunophenotype

The immunohistochemical staining of the abnormal lymphoid infiltrate demonstrated expression of CD3, CD5, CD2 with decreased expression of CD7. The T cells are positive for TCRBF1 and negative for TCRD, perforin, granzyme B, TIA1 and CD30. The proliferation rate is extremely low (Ki-67 <5%). EBV RNA stain is negative**.**

Cytogenetics

None

Molecular Studies

Clonality studies were positive for a clonal T cell receptor gene rearrangement and demonstrate the same predominant 183 bp and 206 bp peaks in the two jejunum biopsies and ileum. The ileum biopsy also showed a predominant polyclonal background indicating an early lesion.

Proposed Diagnosis

Indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract.

Interesting Feature(s)

• The case shows non destructive mucosal and submucosal lymphoid infiltrate that is classically observed in indolent T cell lymphoproliferative disorder (ITLPD) which typically presents as small intestinal lesions.The patient has a history of inflammatory bowel disease which can be seen in patients with ITLPD.

- These lesions usually involve the lamina propria and are non destructive, predominantly CD4 or CD8 positive and can be easily dismissed by a surgical pathologist.
- However, this case demonstrates submucosal involvement and showed decreased expression of both CD4 and CD8, most prominent in the most recent jejunal biopsy.
- The lesions in the jejunum (biopsy 1) and ileum were signed out as no pathologic abnormality but showed the same clonal peaks observed in the recent jejunal (biopsy 2) biopsy.
- Although multiple sites in the GI tract are involved, with chronic persistence of disease, progression of the disease is still not observed. TCR clonality studies confirmed T cell clonal peaks in both the jejunum biopsy sites and ileum. The ileum biopsy also showed a predominant polyclonal background indicating an early lesion

EA4HP24-LYWS-192

Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder.

Dr. Amrit Singh, **Dr. Ifeyinwa Obiorah**

University of Virginia Hospital, Pathology/hematopathology, Charlottesville, USA

Case Description

The patient is an 80 year old male with a history of melanoma, status post excision. He had a recurrence of disease with metastatic disease at skin and lung and was treated with a vaccine trial in complete remission since 2000. In August 2023, the patient developed a new itchy rash at the left forearm/elbow. No other skin lesions were identified. Further imaging studies showed no lymphadenopathy or organomegaly. The lesion was completely excised and sent for pathologic evaluation. Further treatment was not rendered and patient did not show any recurrence 4 months later.

Biopsy Fixation Details

Forearm biopsy. 10% neutral buffered formalin fixed, paraffin embedded sections.

Frozen Tissue Available

None

Details of Microscopic Findings

Examination of the biopsy show skin with a dense superficial and deep dermal polymorphous infiltrate extending focally into the subcutaneous tissue. The infiltrate is composed mostly small to medium sized lymphocytes with ovoid nuclei and compact chromatin. Admixed are numerous plasma cells.

Immunophenotype

The immunohistochemical staining of the abnormal lymphoid infiltrate demonstrated expression of CD20 and CD79a. The plasmacytic component also show expression of MUM1 but are polytypic by kappa and lambda stains. A subset is positive for IgG and IgG4. The atypical B cells were negative for CD10, BCL6 and cyclin D1. BCL2 is positive in both B and T cell areas. There is increased background T cells that are predominantly CD4 positive. A subset show expression of PD1 and ICOS. Ki-67 showed a low proliferative rate (5-10%). EBV RNA stain is negative.

Cytogenetics

None

Molecular Studies

The immunoglobulin heavy chain gene PCR assay of the left forearm biopsy demonstrates predominant 248 bp, 104 bp, and 232 bp peaks within the valid size ranges for tubes B, C, and D, respectively. The T-cell receptor gamma-chain gene PCR assay demonstrates a polyclonal gene rearrangement pattern.

Proposed Diagnosis

Primary cutaneous marginal zone lymphoma/lymphoproliferative disorder favored.

Interesting Feature(s)

- The case shows prominent B cell infiltrate, which is classically observed in primary cutaneous marginal zone lymphoma/ lymphoproliferative disorder.
- However, this case demonstrates prominent T cell infiltrate that is predominantly CD4 positive, which is classically observed in primary cutaneous CD4 positive small/medium T cell lymphoproliferative disorder (PCD4TLPD) which typically presents as localized skin lesions.
- A subset of the T cells showed expression of follicular helper T cell markers such as PD1 and ICOS.
- Although, the plasma cells did not show definite monotypic plasma cells by immunohistochemistry, interestingly, a subset of the plasma cells showed IgG

expression with fewer IgG4 positive plasma cells. IGH clonality studies confirmed clonal peaks in the biopsy with a polyclonal TCR gene rearrangement.

- The biopsy show overlapping features of PCMZL and PCD4TLPD which require a combination of clinicopathological studies for definite diagnosis.

EA4HP24-LYWS-196

Indolent TdT+ T-lymphoblastic proliferation progressed to T lymphoblastic leukemia/lymphoma

Dr. Yulan Jin, Dr. Ling Zhang, Dr. Haipeng Shao, **Dr. Xiaohui Zhang**

Moffitt Cancer Center, Tampa, Tampa, USA

Case Description

The patient is a 73-year-old female who noticed a large right cervical lymph node swelling, followed by CT-revealed extensive lymphadenopathy one year after. The patient was on observation because of indolent clinical course. Five years after the initial presentation (2023),the patient started experiencing generalized weakness, lightheadedness and short of breath, and had worsening lymphadenopathy, developed disseminated intravascular coagulation, acidosis, hypotension, and then deceased. An autopsywas performed.

Biopsy Fixation Details

Lymph node biopsy and the autopsy tissues were fixed in 10% formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Initial lymph node biopsy showed partial effacement of the nodal architecture by paracortical and interfollicular atypical lymphoid cell proliferation, mainly composed of small to medium sized lymphocytes with open chromatin, inconspicuous nucleoli, and streaming growth pattern in the fibrotic background. Residual nodal architecture shows features of regressive follicles, interfollicular plasmacytosis and vascular hyalinization, reminiscent of hyaline-vascular variant of Castleman disease. Initial bone marrow examination was negative.

Autopsy examination showed widespread lymphadenopathy (up to 4.0 cm) and hepatosplenomegaly. Microscopic examination showed T-cell lymphoblastic leukemia/lymphoma involving multiple organs including lung, liver, kidneys, lymph nodes and bone marrow.

Immunophenotype

Lymph node biopsy: The atypical lymphoid cells were positive for CD3, dim CD5, dim CD4, dim CD2, TdT, and CD1a, while negative for CD7, CD8, CD10, ALK1, and EBER. Ki67 showed a high proliferation index (80-90%).

Autopsy: The neoplastic cells were positive for CD3 and CD99 (subset), and negative for MPO, PAX5, CD34 and TdT.

Flow cytometry performed on peripheral blood before the patient died identified an immature T cell populationexpressing partials surface CD3, partial CD2, CD5, CD7, CD99 (subset), CD38, CD13 (subset), and CD33 (subset), and lacking CD34, TDT, CD4, CD8, CD1a, CD19 and MPO.

Cytogenetics

N/A

Molecular Studies

Initial lymph node biopsy: T cell receptor gene rearrangement studies showed polyclonal peaks.

Disease progression: Clonal Tcell receptor beta and gamma gene rearrangements were detected.

Proposed Diagnosis

Indolent TdT+ T-lymphoblastic proliferation, associated with hyaline-vascular variant of Castleman disease, progressed to T-lymphoblastic lymphoma/leukemia

Interesting Feature(s)

Indolent T-lymphoblastic proliferation(iT-LBP) is characterized by non-clonal proliferation of immature T lymphoid cells, with an indolent clinical course requiring no treatment. Literature review shows no report of progression to T lymphoblastic leukemia/lymphoma (T-ALL/LBL).This case has distinctive clinical and histologic presentations, posing a diagnostic challenge. The patient initially exhibited diffuse lymphadenopathy in the setting of Castleman disease, and eventually progressed to T-ALL/LBL after a 5-year indolent course, with an immunophenotype drift. The identification of TdT+ T-lymphoblasts within a hyaline-vascular variant of Castleman disease background suggests a potential association between immune dysregulation environment and development or/and transformation of iT-LBP. The unique two-phase presentation of this case from iT-LBP to T-ALL/LBL can help us better understandthis entity.

EA4HP24-LYWS-211

Diffuse large B cell lymphoma (DLBCL) in a patient with Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract treated with cyclophosphamide and methotrexate

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Case Description

42-year-old male with >10 year history of malabsorption and intestinal subocclusion episodes. Initially, refractory celiac disease was suspected, receiving steroids and azathioprine without improvement. In 2008 a subocclusive episode required partial resection of jejunum, pathological study reported Intestinal T-cell lymphoma without atrophic mucosa. As diagnosis was inconsistent with clinical background, he only received supportive measures with general improvement, but malabsortion and subocclusive episodes persisted. He was referred to our hospital, previous biopsies were reviewed and an endoscopic biopsy was obtained. Endoscopy showed atrophic and pseudonodular mucosa from the duodenal bulb throughout the explored segment. Diagnosis of T-cell CD8+ lymphoproliferative disease was confirmed, with TCR monoclonal rearrangement. In 2016 he received methotrexate for 8 months with temporary response, subsequently changed to cyclophosphamide with clinical and radiological improvement. In 2021 he presented with bulky abdominal mass causing small intestine stenosis, requiring surgery. Pathological study showed infiltration by DLBCL along with infiltration by the previously reported atypical T-cell population. Staging bone marrow biopsy showed infiltration by both lymphoproliferative disorders. He received R-CHOP and methotrexate (CNS profilaxis) with DLBCL complete remission.

Biopsy Fixation Details

Formalin-fixed paraffin-embedded

Frozen Tissue Available

No

Details of Microscopic Findings

2008 Ileal mucosa with atypical and monotonous lymphoid infiltrate extending into lamina propria, without lymphoepithelial lesions nor enteropathy signs.

2021 Diffuse infiltration of lamina propria and muscular layer by large occasionally pleomorphic lymphocytes with mucous ulceration, extensive necrosis, numerous mitosis and apoptotic cells. Occasional intermingled accompanying small lymphocytes. Adjacent preserved mucosa with dense infiltration of lamina propria by atypical mature-looking lymphocytes, encompassing some lymphoid nodules at the base of the infiltrate.

Immunophenotype

2008

Atypical cells CD2, CD3, CD5 and CD7+. CD8α and CD8β coexpression. TCRβ+ TCRγ-. TIA1+. CD4, granzyme B, CD56 and EBER -. Ki67 5-10%.

2021

Large cells CD20, CD79a, PAX5, CD10, BCL6 and MUM1 +. Ki67 >90%. CD30 patchy and weak. MYC 40%+. p53 diffusely+. EBER-. No follicular dendritic pattern with CD21.
Small lymphocytes CD3, CD5, CD2, CD7 and CD8 +. CD4+ in a scattered and extensive manner. TCRβ+ TCRδ-. TIA1+. Granzyme B and CD56-. Residual follicular dendritic patterns in the basal part of the atypical T-cell infiltrate with CD21.

Cytogenetics

2021

BCL6, MYC, IRF4 BAP normal (FISH) BCL2 not evaluable

Molecular Studies

2008 TCRγ monoclonal rearrangement (PCR)
2021 TCRγ and β monoclonal rearrangement (PCR). Ig light chain rearrangement monoclonal; IgH polyclonal (FR3, FR1 and FR2)

Proposed Diagnosis

2008 Indolent clonal T-cell lymphoproliferative disorder (CD8+) of the gastrointestinal tract
2021 DLBCL germinal center phenotype, and Indolent clonal T-cell lymphoproliferative disorder (CD8+) of the gastrointestinal tract

Interesting Feature(s)

Despite the nature of T-cell indolent lymphoproliferative syndromes, cases of transformation to peripheral T-cell lymphoma or large T-cell lymphoma have been described. Coexistence of DLBCL with indolent T lymphoproliferative syndrome of the gastrointestinal tract has only been described once in the literature. In this case, the B-cell lymphoma could be related to previous treatment with methotrexate.

EA4HP24-LYWS-212

An Indolent Peripheral Blood T-cell Clone Associated with Protracted Eosinophilia

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Case Description

79-year-old female with a past medical history of lung adenocarcinoma and persistent unexplained eosinophilia since the 1960s. Bone marrow studies in 2011 that showed no overt evidence of a hematolymphoid neoplasm. However, TRG gene rearrangement studies done in 2017 on two blood specimens revealed monoclonal rearrangements.

Biopsy Fixation Details

Bone marrow core biopsy: fixed in zinc formalin, decalcified in formical.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Bone marrow aspirate: mildly increased eosinophils with no significant cytologic atypia, megakaryocytes with mild atypia (small, hypolobated forms) in ~10%. Lymphocytes are morphologically unremarkable and normal in number. Mast cells are unremarkable. Blasts were not increased.
Bone marrow clot and biopsy: normocellular marrow with mildly increased eosinophils. Single well-circumscribed aggregate of small lymphocytes with no overt atypia in the clot section. Megakaryocytes with mild atypia (small, hypolobated forms) in ~10%. A reticulin stain did not show fibrosis.

Immunophenotype

Immunohistochemistry (bone marrow): few scattered and occasionally clustered small CD2+ CD3+ CD4+ CD5+ CD7(partial)+, CD25(minor subset)+ GATA3(subset)+ CD8- CD10- CD30- BCL6- PD1- ALK- T-cells.
Flow cytometry (bone marrow aspirate and peripheral blood): minute surface CD3- CD7- CD2+ CD5 (bright)+ CD4+ CD8- CD16- CD56- CD57- TCRa/b- TCRg/d- CD25- CD30- aberrant T cell population (<1% of total events).

Cytogenetics

- Normal female karyotype: 46,XX[20]
- FISH studies: negative for *PDGFRA, PDGFRB, FGFR1 and JAK2* rearrangements.

Molecular Studies

- TCR gene rearrangement studies by NGS (peripheral blood and bone marrow, 2023): Positive for identical clonal rearrangements.
- Massively parallel gene sequencing studies: no disease-associated variants or variants of uncertain significance.

Proposed Diagnosis

Lymphocytic variant of hypereosinophilic syndrome (L-HES)

Interesting Feature(s)

L-HES is a rare subtype of secondary hypereosinophilic syndrome, characterized by peripheral blood and tissue eosinophilia mediated by an aberrant T-cell clone that produces elevated amounts T helper-2 cytokines. Given its rarity, it is likely an underdiagnosed disease. In fact, our patient was diagnosed with the disease only after several decades of unexplained eosinophilia. Our case emphasizes the need for increased awareness of the disease among pathologists and other healthcare providers. Although L-HES typically behaves indolently despite frequent nodal and extranodal dissemination of clonal T-cells, there is an increased risk of transformation to an overt lymphoma, therefore, these patients need to be followed up regularly. In summary, our case demonstrates that in the appropriate clinical context, a combination of clinical suspicion, flow cytometric evaluation, and TCR gene rearrangement studies can help the identification of aberrant clonal T-cells, facilitating a diagnosis of L-HES in patients with otherwise unexplained eosinophilia.

EA4HP24-LYWS-215

An atypical thymic hyperplasia

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Case Description

39-year-old woman with persisting extrasystoles, hyperthyroidism not-otherwise specified and vitiligo underwent cardiac magnetic resonance and then computed tomography (CT) scan. No antibodies against nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction were found.

CT scan confirmed the presence of a 30 mm-sized mass in the anterior-superior mediastinum, suspicious for thymic neoplasia. FDG-positron emitting tomography (PET) identified increased uptake (SUV 4.1), being limited to the thymic lodge.

Thymectomy was performed: the specimen was not weighted at grossing, but it consisted of adipose tissue with foci of well-developed thymic gland lobules, in absence of recognizable nodular solid lesions.

Biopsy Fixation Details

10% buffered formalin fixed; paraffin embedded.

Frozen Tissue Available

No

Details of Microscopic Findings

At scanning magnification, the specimen consisted of residual thymic gland with substantially preserved lobular architecture and minor signs of true-type hyperplasia (no evidence of follicular lymphoid hyperplasia) and foci of disruption of the cortex along with hemorrhage. The latter featured a derangement of the cytokeratin+ epithelial and CD34+ endothelial meshwork, in association with a confluent proliferation of small lymphoid cells without atypia, consisting of CD4/CD8 double positive, cortical thymocytes.

Immunophenotype

The atypical proliferation featured a phenotype consistent with double positive, cortical thymocytes: CD2+, sCD3+, CD5+, CD7+, CD4+, CD8+, TdT+, CD1a+, CD10-, CD34-, CD117-, CD79a-, LMO2-, Ki67 60%. In the medullary area, small aggregates of CD79a+ B-cells were observed.

Cytogenetics

Not performed

Molecular Studies

Clonality analysis for *TCRG* rearrangement (BIOMED-2 guidelines): polyclonal.

Proposed Diagnosis

Atypical thymic hyperplasia with features of indolent T-lymphoblastic proliferation (IT-LBP, WHO 2022).

Interesting Feature(s)

A significant fraction of clinically asymptomatic / lacking "thymus specific" symptoms patients, with enlarged thymus, receives a histologic diagnosis of “normal thymus” after thymectomy. In our case, in the context of a purported autoimmune background, but with thymic PET uptake, microscopic examination revealed a thymus with mostly unremarkable features, but with foci of altered architecture in form of disruption of the haemato-thymic barrier and hemorrhage, the latter not being entirely attributed to the surgical manipulation. In this context, a confluent expansion of cortical thymocytes, not fully diagnostic for T-lymphoblastic neoplasm, is observed.

The histologic picture suggests a pattern of thymic hyperplasia with atypical features, in form of lysis of the cortical endothelial and epithelial structure with extracortical expansion of lymphocytes, akin to paracortical hyperplasia of lymph nodes and to some extent fulfilling the histologic criteria for a diagnosis of IT-LBP.

IT-LBP is usually regarded as an extra-thymic TdT+ proliferation, mostly identified incidentally in localized lymphadenopathies / masses in otherwise healthy individuals or in association with apparently unrelated diseases (neoplasms, autoimmune). Our case documents an unprecedented pattern of intrathymic proliferation of polyclonal, CD4+/CD8+ T-lymphoblasts with some disruption of the functional architecture of the gland, which could be even prodromal to peripheral IT-LBP and whose relationship with autoimmune-mediated disorders cannot be completely ruled out.

EA4HP24-LYWS-229

Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder

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Case Description

A 41-year-old male presented with an asymptomatic right superior helix ear lesion that had progressively increased in size over one-year duration.

Physical exam revealed a 6 mm pearly pink papule with central telangiectasis. The clinical differential diagnosis included basal cell carcinoma vs. other neoplasms.

CT imaging studies showed no evidence of concurrent lymphadenopathy or hepatosplenomegaly.

The patient received localized external beam radiation therapy at a dose of 30 Gy in 15 fractions. Clinical follow-up has revealed no evidence of recurrent/residual disease one year status post radiation therapy.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

H&E stained slides demonstrated a superficial shave biopsy of skin with a diffuse dermal infiltrate composed of small-to-intermediate sized atypical lymphocytes with irregular nuclear contours, fine chromatin, eosinophilic cytoplasm, and inconspicuous nucleoli. Admixed plasma cells were noted. A Grenz zone was present and the epidermis was uninvolved and unremarkable.

Immunophenotype

The neoplastic T-cell infiltrate was diffusely positive for CD3 and CD8 with diminished CD2 and partially diminished CD5 expression. CD7 showed retained expression. CD68 (Golgi dot-like pattern) and BCL2 were positive. The neoplastic T-cells were negative for CD4, CD10, CD30, BCL6, TIA-1, Granzyme B, and perforin. CD20 highlighted singly scattered small B-cells and rare, small B-cell aggregates. CD21 did not highlight any follicular dendritic cell meshworks. The Ki-67 proliferative index was low in the neoplastic cells (<10%).

Cytogenetics

N/A

Molecular Studies

T cell gene receptor (TCR) studies performed on the right super helix shave biopsy showed clonal peaks in TCR beta by BIOMED2 PCR and dominant TCR gamma rearrangement sequences by NGS.

Proposed Diagnosis

Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder

Interesting Feature(s)

This case represents a classical presentation of a rare entity (<1% of all primary cutaneous lymphomas/lymphoproliferative disorders). Interesting morphologic/immunophenotypic features include the presence of a Grenz zone and positive CD68 with Golgi dot-like pattern.

EA4HP24-LYWS-241

An Unusual Case of Primary Marginal Zone Lymphoma of Class-Switched Type, IgG4-Positive, Presenting with Skin and Conjunctival Lesions

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Case Description

A 65-year-old woman with a history of melanoma of the left upper thigh in 2014, was treated with nivolumab followed by T-VEC plus pembrolizumab, completed by 02/2023. In 01/2020, she dveloped skin lesions on left upper arm. The skin biopsy was felt to be consistent with primary cutaneous marginal zone lymphoma (MZL) of class-switched type. She received 2400 cGy in 12 fractions with resolution of the skin lesion. Subsequently, she experienced a slowly progressive conjunctival/scleral lesion in her right eye, first noted at approximately 10-12 months ago. She had no B-symptoms or palpable adenopathy. A staging CT was negative. Her CBC was within normal ranges. No serum paraprotein was identified. An incisional biopsy of right conjunctival lesion was performed (9/29/2023).

Biopsy Fixation Details

The biopsy was formalin fixed and paraffin embedded.

Frozen Tissue Available

N/A.

Details of Microscopic Findings

Skin, left upper arm, punch biopsy: H&E-stained sections show a patchy dense lymphoid infiltrate composed of germinal centers surrounded by mantle/marginal zones and expanded T cells. Mature plasma cells are noted at the edge of the follicles.

Conjunctival lesion, incisional biopsy: H&E-stained sections show scattered attenuated germinal centers of varying size surrounded by expanded mantle/marginal zones. There are patchy aggregates of plasmacytoid/plasma cells at the periphery of mantle/marginal zones. A large cell population is not seen. Significant fibrosis is not present.

Immunophenotype

Skin, left upper arm, punch biopsy: Limited IHC panel was performed due to tissue exhaustion. Plasma cells at the edge of the nodular infiltrate show kappa light chain restriction on in situ hybridization (ISH). MUM1 shows scanty plasma cells in one of the tiny residual tissue fragments. These cells express IgG4 and IgG (weak) without IgM and IgD.

Conjunctival lesion, incisional biopsy: By immunohistochemistry, the expanded mantle/marginal zone B cells are positive for CD19, CD20, CD79a, BCL2 (strong), LMO2 (weak), PAX5, MNDA (subset, variable), IgD, and IgM (weak). The surrounding plasmacytoid/plasma cells are positive for CD19 (weak), CD79a, CD138, MEF2B (weak) and IgG with co-expression of IgG4 and show kappa light chain restriction. These

plasmacytoid/plasma cells are negative for CD20, PAX5, IgD, and IgM (Image 2). B cells are negative for cyclin D1 and SOX11. HHV8 is negative. EBER ISH is negative.
Flow cytometry of conjunctival lesion: 1.6% kappa restricted B cell population positive for CD10, CD20, and CD38 (increased) without co-expression of CD5 and CD200, compatible with follicular hyperplasia. There were abundant polytypic B cells in the background.

Cytogenetics

N/A.

Molecular Studies

Polyclonal immunoglobulin gene rearrangement by PCR.

Proposed Diagnosis

Extranodal marginal zone lymphoma, class-switched type, IgG4-positive.

Interesting Feature(s)

- Heavy chain class-switched primary cutaneous MZL with IgG4 overexpression is one histologic subtype of primary cutaneous MZL with an indolent nature; extracutaneous site involvement is rare.
- Here, we present an unusual case with a prior diagnosis of class-switched primary cutaneous MZL, who subsequently developed a slow-growing conjunctival lesion with features consistent with extranodal MZL, class-switched type, IgG4-positive.
- This case contributes to the growing understanding of primary cutaneous MZL, particularly the class-switched, IgG4-positive subtype. It emphasizes the need for further study to explore the clinical and pathological features of this subtype, especially those involving extracutaneous sites.

EA4HP24-LYWS-250

EBV-associated T-cell Lymphoproliferative Disorder in a Young Adult

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Case Description

A 23-year-old healthy Hispanic male presented with right lip lesion, treated with local therapy. He developed persistent fever resistant to conventional therapies, facial swelling, blisters on abdomen and thigh, which rapidly progressed to black necrotic ulcered lesion within few weeks. No h/o drug allergy, trauma or mosquito bite. Skin punch biopsy was performed.

Lab Data Summary:

CBC: Hb 9.6g/dl, Hct29%, WBC4.6 Thou/ul, Plt 60Thou/ul
High ferritin, triglycerides, LDH, and LFT's. Slightly high fibrinogen

CT abdomen and pelvis showed hepatic lesion, stomach with soft tissue thickening and irregularity, normal spleen and no LN's

Biopsy Fixation Details

Fixed in 10% NB formalin.

Frozen Tissue Available

N/A

Details of Microscopic Findings

Skin with dense dermal and focal subcutaneous atypical lymphoid infiltrate composed of pleomorphic medium-sized to large cells with fine chromatin, inconspicuous nucleoli, and scant cytoplasm. Epidermotropism is present. The infiltrate shows an angiocentric growth pattern with focal angioinvasion. Frequent apoptosis and coagulative necrosis are present.

Immunophenotype

Atypical lymphoid cells are CD2+ CD3+ CD8+ CD5(subset)+ CD30(subset)+ EBER(ish)+ CD7- CD4- ALK1- CD20-

Cytogenetics

N/A

Molecular Studies

Clonal T-cell Gamma rearrangement detected.

Next Generation Sequencing:

Variants of uncertain significance

DDX3X 52%

GNAS 46%

PTPN11 50%

Proposed DiagnosisEBV associated CD8+ T-cell lymphoma.

Differentials:

Extranodal NK/T cell lymphoma

- Infiltration of extranodal tissues (skin) by lymphoma cells with variable morphology and presence of angioinvasion and angiodestruction
- Cytotoxic T cell phenotype and positive for EBER

EBV associated lymphoproliferative disorder (LPDs) of childhood

- Hydroa vacciniforme lymphoproliferative disorder, systemic form
- Systemic EBV positive T-cell lymphoma of childhood

- Young age group without immunodeficiency and high EBV viral load
- Skin eruptions followed by persistent systemic manifestation like fever, hepatomegaly and GI infiltration
- Multi-organ infiltration by EBV+ atypical cytotoxic T cells with angioinvasion and angiodestruction

Clinical Course:

• High EBV viral load detected by PCR after skin biopsy.

• Bone marrow biopsy x 2 showed normocellular marrow with trilineage hematopoiesis. No overt evidence of lymphoma or hemophagocytosis. However, TRG rearrangement was positive same as on skin.

• Patient completed two cycles of chemotherapy.

• After three weeks, patient presented with hematemesis. Endoscopy showed gastric

perforation and gastric ulcer. Stomach fundus biopsies were collected and omental (Graham) patch was placed. H&E and IHC show EBV+ CD8+ Mature T cell lymphoma, morphologically similar skin.

Interesting Feature(s)

• EBV+ T/NK cell LPD's of childhood are rare.
• These entities are challenging and difficult to define specific category.
• Our patients clinical and morphologic findings could fit into more than one category of EBV-associated LPD's.
• Multiparameter approach including clinical information, morphologic and immunophenotypic features are required for diagnosis.
• Regardless of specific entity, the patient was initially treated with chemotherapy. As the disease progressed, he was switched to another chemotherapy regimen.
• EBV+ T/NK cell lymphoproliferative disorders of childhood are usually chemoresistant and often with fatal outcome. Our patient showed an excellent response to chemotherapy DDGP (cisplatin, dexamethasone, gemcitabine, and pegaspargase) regimen and waiting for transplant.
• Our case is an example that there is lack of markers to reliably predict clinical behavior in these disorders.

EA4HP24-LYWS-253

Indolent T-cell lymphoma /clonal lymphoproliferative disorder of the gastrointestinal tract - a mimic of coeliac disease/ gluten sensitive-enteropathy

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Case Description

62 year old man, with 7 year history of malabsorption symptoms (chronic diarrhoea, weight loss) attributed to gluten sensitive enteropathy (GSE), presented in 2013 for worsening diarrhoea. OGD & colonoscopy revealed extensive flattening of duodenum. Duodenal & ileal biopsies were diagnosed as peripheral T cell lymphoma (PTCL-NOS), with a comment that this case appeared indolent, but was thus labelled as it did not fit any of the known TCL entities at the time based on WHO 2008(3e). PET-CT showed intense FDG-avid nodular thickening of colon, segments of small bowel. He underwent 3 cycles each of EPOCH, ICE, & autotransplant BEAM. Subsequent PET-CT showed less FDG uptake, deemed as partial response.He was in remission until his presentation 8 years later(2021) with diarrhoea & weight loss despite a gluten-free diet. His anti-gliadin & anti-endomysial antibodies were negative. OGD showed scalloped appearance of duodenum suggestive of villous atrophy; colonoscopy was normal.

Biopsy Fixation Details

Neutral buffered formalin, 24-48 hours

Frozen Tissue Available

-

Details of Microscopic Findings

The 2013 & 2021 duodenal biopsies showed severe villous blunting, focal minimal intraepithelial lymphocytosis & lamina propria expansion by a dense non-destructive infiltrate of mostly small lymphocytes, a few plasma cells, eosinophils. The ileal biopsies are similar, except for preserved villous architecture.

Immunophenotype

The duodenum & ileum show lamina propria expansion by CD3,CD2+ small T lymphocytes, CD4+,CD8-,TCR-βF1+, & loss of CD5,CD7. The T cells are TCR-γδ, TIA-1, granzyme B, CD56 negative. The proliferation index by Ki67 is ≤5%, in keeping with an indolent process. Kappa & lambda in-situ hybridization reveal a polytypic plasma cell population. A few CD20,PAX5+ B cell aggregates are present, outlined by CD21,CD23+ follicular dendritic meshworks, which are not expanded or disrupted.

Cytogenetics

-

Molecular Studies

TCR-G & B PCR showed monoclonal products in TCRG tube A 209bp,TCRB tube A 255bp,tube B 268bp,tube C 186bp

Proposed Diagnosis

Indolent T-cell lymphoma of the gastrointestinal tract (WHO 5e)/ Indolent clonal T-cell lymphoproliferative disorder (LPD) of the gastrointestinal tract (ICC)

Interesting Feature(s)

This case illustrates the resemblance of indolent TCL-GIT to GSE clinically, endoscopically & histologically (villous blunting, non-destructive lymphoid infiltrate). The few clues that led to workup for a neoplastic process in 2013 were the relative lack of epitheliotropism (highly unusual for GSE) & mild atypia.

GSE is very rare in Asians, & lack of response to gluten-free diet, absence of anti-gliadin & anti-endomysial antibodies should have raised doubts of GSE. Since indolent TCL-GIT was not an established entity in 2013, & clinical & histologic features were not in keeping with recognized TCL entities at the time, it was categorized as PTCL-NOS. Although it was highlighted that this case appeared indolent & resembled the few case reports of indolent T-LPD, the patient was given chemotherapy.

Indolent T-cell LPD was formally introduced in WHO 2017(4e). This diagnosis was appropriately rendered in the 2021 biopsies. Upon multidisciplinary review, he was deemed not to have GSE as the symptoms & endoscopic features could be attributed to indolent TCL-GIT.

Given its rarity, the importance of its recognition & distinction from commoner, more aggressive GIT TCLs such as EATL, MEITL & intestinal TCL, NOS, cannot be overemphasized to avoid over-treatment.

The protracted & relapsing clinical course of indolent TCL-GIT without transformation to more aggressive lymphoma so far attest to its indolent nature.

EA4HP24-LYWS-256

Indolent Clonal T-cell Lymphoproliferative Disorder of the Gastrointestinal Tract with Clusters of NK-cells.

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Case Description

A 66-year-old man presented in November 2023 with intestinal obstruction. The patient had a history of chronic diarrhea spanning 10 years. Celiac disease and autoimmune processes were ruled out. The laboratory analysis was normal, without lymphocytosis. The resection of a segment of the small bowel was performed. Samples of the bowel and a mesenteric lymph node were submitted to the workshop.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

The *lamina propria* is expanded by a dense lymphocytic infiltrate that extends into the *submucosa* and the muscular layer. Severe villous atrophy is evident. No significant epitheliotropism is seen. The mesenteric lymph nodes are affected by the same lymphocytic infiltrate with minimal atypia. Angioinvasion/destruction and necrosis are absent.

Immunophenotype

The lymphocytes express CD3, CD5, CD7 and CD8. CD4 is partially positive. TIA-1 is positive. The Ki-67 proliferation index is low (less than 5%). TdT, CD34, CD20 and CD30 are negative. TCL-1 is pending. Subepithelial plasma cells are polytypic. EBER is negative.

In the lamina propria, the presence of clusters of lymphocytes expressing CD56 and C-kit was notable, suggesting that they could be accumulations of NK cells. CD57 and EBER are negative.

The same population is detected in the mesenteric lymph node.

Cytogenetics

Not performed.

Molecular Studies

T-cell receptor (TCR) beta (BIOMED-2) clonality analysis studies are monoclonal.

Proposed Diagnosis

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract with clusters of NK-cells.

Interesting Feature(s)

Our case is an example of an indolent T-cell lymphoproliferative disorder of the gastrointestinal tract, presenting findings that make it intriguing.

On the one hand, histologically, it is accompanied by severe villous atrophy, infiltration of all the layers of the intestinal wall, and extension to regional lymph nodes.
Additionally, it is surprising that large clusters of mature NK-cells are identified in the *lamina propria* and in the mesenteric lymph node, raising questions about whether they are physiological groups of NK-cells or if it could be a mixed case of indolent T and NK-cells.

EA4HP24-LYWS-266

Proliferation of immature TdT+ lymphocytes in an extrathymic location associated with Unicentric Castleman's Disease

Dr. Peggy Dartigues[1], Dr. Veronique Meignin[2], Dr. Muriel Hourseau[3]

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Case Description
40-year-old woman with no previous medical history. incidental discovery on CT and MRI scans, following a road traffic accident, of a 60 x 40 mm tissue mass, in contact with the left psoas muscle and the left primitive iliac artery, with regular contours and homogeneous enhancement, respecting adjacent structures. Hypothesis: adenopathy, paraganglioma, solitary fibrous tumour, etc
Biopsy Fixation Details
A centimetric needle fragment fixed in formol followed by partial surgical removal of the inguinal mass
Frozen Tissue Available
yes
Details of Microscopic Findings
Needle biopsy and surgical specimen shared the same microscopic features with small lymphoid nodules, without identified germinal centres, separated by renriched vascularised, polymorphous areas containing mature lymphocytes, a few histiocytes and plasma cells as well as areas of small to medium lymphoid cells with fine chromatin, non-atypical, non-mitotic, immature/blastic in appearance. Surgical specimen analysis highlighted lymphoproliferative lesion caracterized by changes in the follicular and interfollicular components, with regressed germinal centers surrounded by hyperplastic mantle zone (« onion skin » like), containing few blood vessels with hyalinised walls. Expansion of the interfollicular stroma included immature lymphoid proliferation.
Immunophenotype
AE1AE3, desmin, STAT6, PS100, neuroendocrine markers, HHV8 and EBER -. The CD20+ B lymphoid nodules were separated by internodular T areas expressing CD2, CD3, CD5, CD7, CD4 and CD8, with CD1a+, CD10+ and TDT+ suspect lymphoid cells. The Ki67 proliferation index was high: 90%.

Cytogenetics
Normal karyotype (tissue and blood)
Molecular Studies
Not done
Proposed Diagnosis
Unicentric Castleman's disease with indolent T lymphoblastic proliferation
Interesting Feature(s) Proliferation of immature TdT+ lymphocytes in an extrathymic location without invasion of the bone marrow and blood, which may be associated with other pathologies including Unicentric Castleman's Disease (but also with a follicular dendritic cell tumour, angioimmunoblastic T lymphoma, acinar cell carcinoma, hepatocarcinoma, autoimmune pathology (rheumatoid arthritis). **Be aware of these diagnosis and do not over-diagnose T lymphoblastic NHL**. Be careful with microbiopsies, requiring clinical and molecular comparison.
References : *Brar, Histopathology, ,2020 ; Ohgami, Adv Anat Pathol, 2013 ; Ohgami; Am J Surg pathol 2012 ; Ohgami, Am J Surg Pathol, 2014 ; Pizzi, Hum Pathol 2018 ; Velankar, Am J Surg Pathol 1999*

EA4HP24-LYWS-276

Indolent T-cell lymphoproliferative disorder clinically presenting as meningitis

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Case Description
A 21-year-old male with celiac disease presented with nausea, vomiting, headache, neck pain, confusion and mild photophobia of 3-day duration, consistent with meningitis. He reported low-grade fever, flu-like symptoms and headache for ten days before admission. Laboratory tests revealed neutrophilia and positivity for ANA and anti-DNA antibodies. A spinal tap revealed macroscopically clear fluid with normal glucose and slightly increased protein levels. Spinal fluid culture did not document bacterial growth. PCR for viral infections was positive only for HHV-7. Spinal fluid flow cytometry disclosed 72% T-cells with aberrant phenotype (CD3+/CD5+/CD2+/CD7-/CD4-/CD8-/CD56-/CD57-+/TCRγδ-/TCRαβ+) and TCRVβ 7.1 restriction. The same atypical population was identified in the peripheral blood (29% of total lymphocytes) and bone marrow (15% of total cells). Clonality tests on peripheral blood disclosed oligoclonal *TCR* rearrangement without *STAT3* and *STAT5b* mutations. Genetic screening for autoimmune lymphoproliferative syndrome (ALPS) was negative. Total-body PET-RM identified multiple PET-avid lymphadenopathies (SUV max

10), which were submitted for histological evaluation (axillary and inguinal lymph node). After the diagnosis, steroid-based and anti-viral therapy led to prompt resolution of the neurological symptoms with persistent circulating atypical T-cells. Steroids were discontinued following 3-month tapering. At present (32 months after clinical onset), the patient is alive and in good clinical conditions without any need of further therapy.

Biopsy Fixation Details

The lymph nodes were fixed in formalin.

Frozen Tissue Available

n.a.

Details of Microscopic Findings

Microscopic examination of the lymph nodes showed paracortical expansion by a lymphoid infiltrate consisting of small lymphocytes with mildly irregular nuclear contours and clumped chromatin. Residual primary and secondary follicles and a focal area of necrosis surrounded by epithelioid histiocytes were also present.

Immunophenotype

Immunohistochemical analysis of paracortical lymphocytes showed diffuse positivity for CD3, CD2, CD5 and negativity for CD7, CD4, CD8, TCL1, CD30, ALK1, TdT, CD1a, CD34 and Bcl6. CD20 was positive in accompanying B-cells with partial marginalization of follicles. The Ki67 proliferation index was low (5-7%) and *in situ* hybridization for EBV (EBER) was negative.

Cytogenetics

Not performed on lymph node biopsy.

Molecular Studies

Clonality tests on the inguinal lymph node showed monoclonal *TCRγ* rearrangement. Molecular tests on peripheral blood disclosed no *FAS*, *STAT3* and *STAT5b* mutations.

Proposed Diagnosis

Indolent CD4/CD8-negative T-cell lymphoproliferative disorder, occurring in a dysimmune setting (celiac disease and positivity for autoimmune antibodies).

Interesting Feature(s)

This case highlights the unusual features of an indolent T-cell lymphoproliferative disorder, primarily presenting with meningitis symptoms together with peripheral blood, bone marrow and lymph node involvement. The overall presentation and phenotype of T-cells posed the differential diagnosis with ALPS, which was excluded by genetic tests for *FAS* mutations and by the negativity for CD7. T-cell large granular lymphocytic leukemia was also excluded by the clinical presentation, T-cell phenotype (CD4-/CD8-/CD57-+) and molecular studies (lack of *STAT3* and *STAT5b* mutations). Short course therapy with steroids prompted durable clinical remission, suggesting the value of conservative therapies for such indolent T-cell proliferations.

EA4HP24-LYWS-287

CD16dim NK-LGLL in a patient with chronic lymphocytosis and a history of mb. Crohn

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Case Description

77 year old male with a history of mb. Crohn since 2008 treated with vedolizumab every 8 weeks. In addition DM2, hypertension and coronary heart disease. Since 2017 fluctuating lymphocytosis between 5.08 -10 x10E9 and 1.09x10E9 smudge cells. No B-symptoms and patient was doing well. No anemia or neutropenia. After diagnostic work up, no treatment was initiated.

To rule out CLL, peripheral **blood** was submitted to Dep. Pathology, Zealand University Hospital. Blood smear revealed lymphocytosis (59%) with medium sized atypical lymphocytes, some with irregular nuclei. Variable abundant granulated cytoplasm.

Initial flow cytometry analyses on blood performed at ZUH with following tubes:

LST1: CD45, CD19, CD20, CD5, CD38, kappa, lambda, CD3, CD4, CD8, CD56

LST2: CD45, CD19, CD20, CD10, CD79b, CD34, CD200, CD23

LST4: CD45, CD3, CD4, CD8, CD5, CD7, CD2, cyCD3

69% lymphocytes with 0.8% B-cells, 9% T-cells with CD4/CD8 ratio 2.7. 29% granulocytes. 88% of lymphocytes positive in CD2, CD7, CD45var, CD38var. Negative in CD3, cyCD3, CD4, CD8, CD5, CD34. These cells were suspicious for NK cells.

Extended flow cytometry analyses on blood performed at OUH with following tubes:

LST: CD45, CD19, CD20, CD56+IgK, CD8+IgL, CD3, CD5, CD38,

NK-CLPD-1-3: CD45, CD3, CD19, CD56, CD2, CD5, CD7, CD26, CD11c, CD16, CD25, CD57, HLA-DR, CD94, cyGranz, cyPerfor

Flow cytometry showed leukocyte count of 14.7 x10E9 with 0.6% B-cells with normal immune profile and 7.5% T-lymphocytes with normal immunophenotype and normal CD4/CD8 ratio (3.5). There was an increased NK cell population of 57.4% with normal expression of CD56, CD2, CD7, CD11c, CD57var and CD94. Notably, a decreased expression of CD16, granzyme B and perforin, as well as overexpression of HLA-DR. They were negative for surface CD3, CD19, CD5, CD26 and CD25.

Upon blood findings, a **bone marrow** investigation was performed. It revealed increased cellularity and increased infiltration of CD2, CD7, TIA and perforin, granzym B pos cells. Perforin was more abundant than granzyme B and TIA. CD56 was sparsely and weakly expressed and more cells stained in CD57. Infiltration was intrasinusoidal and under 5%. Flow cytometry showed 21% lymphocytes and 81% of these had NK cell phenotype as described in blood performed at ZUH.

Biopsy Fixation Details
<24 hours
Frozen Tissue Available
No
Details of Microscopic Findings
Please see case description
Immunophenotype
Extended flow cytometry analyses showed leukocyte count of 14.7 x10E9 with 0.6% B-cells with normal immune profile and 7.5% T-lymphocytes with normal immunophenotype and normal CD4/CD8 ratio (3.5). There was an increased NK cell population of 57.4% with normal expression of CD56, CD2, CD7, CD11c, CD57var and CD94. Notably, a decreased expression of CD16, granzyme B and perforin, as well as overexpression of HLA-DR. They were negative for surface CD3, CD19, CD5, CD26 and CD25.
Cytogenetics
ND
Molecular Studies
Targeted NGS performed on blood and bone marrow detected TET2 c.3311_3312dupTT, p.Ile1105fs, likely pathogenic mutation (VAF 37% blood and 28% BM) and TNFAIP3 c.346C>T, p.Gln116*, likely pathogenic mutation (VAF 5% blood and 4% BM). Mutations in blood and bone marrow were identical. No STAT3 mutations were found.
TCR clonality testing on bone marrow cloth was negative.
Proposed Diagnosis
NK-LGLL (WHO5) or chronic lymphoproliferative disorder of NK cells (ICC)
Interesting Feature(s)
Full work up with extended flow cytometry and mutation analyses that is consistent with NK neoplasm. Flow cytometry work adds to current knowledge of this rare disease. The NK population was CD16dim, granzb dim, perforin dim and HLA-DR bright.

EA4HP24-LYWS-290

Neoplasms with indolent behaviour/primary cutaneous lymphoproliferative disease

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Case Description
44-year-old man presented with an itchy, painful 1,5 cm large plaque on the head, at the fronto-parietal region that was suspected to be associated with an insect bite. Despite of Doxicicline/antibiotic treatment the lesion further enlarged to a 1,5- 2 cm large plaque.

Surgical excision was performed. Laboratory findings: Borrelia IgM, IgG neg., Clamidia pneumoniae IgM neg., IgG pos.

Biopsy Fixation Details

Biopsy fixation: 4% formalin. Frozen tissue is not available. Staging procedure included flow cytometry of the peripheral blood with negative result and ultrasound, that detected a single, slightly enlarged 12x5 mm supraclavicular lymph node, the picture suggested reactive nature. Follow up time was 16 months, after surgical resection the patient is in complete remission (CR).

Frozen Tissue Available

-

Details of Microscopic Findings

Histology revealed dense, tumour-like lymphoid infiltrate filling up the whole dermis, composed of mainly small- to medium sized cells. In the superficial layers the infiltrate had a diffuse appearance, in the deeper parts nodular infiltrate was seen with few compressed germinal centres (GC). Single, scattered medium sized atypical cells with nucleoli and clear cytoplasm were seen.

Immunophenotype

confirmed around 45% CD20+ B and 55% CD3+ T cells. Bcl-6 positive B cells located exclusively in the compressed germinal centres. CD4+/CD8 T cell ratio was 4:1. PD1 expression found in 20% of the cells and rosette formation was observed around large cells. CD30 was negative. FDC network was identified in the middle of the B-cell nodules in the deeper parts of the lesion. Ki67 positivity was around 25%, beside the positive GC cells scattered medium-to large cells were observed.

Cytogenetics

-

Molecular Studies

IGH and TCR gene rearrangement analysis was performed for clonality assessment using the BIOMED−2 Concerted Action protocol as a part of routine diagnostic workup using the IGH VH-JH FR1, FR2 and FR3, and TCR beta (TCRB) primer sets. Monoclonal T-cell receptor gamma chain rearrangement was identified with primer set A: (VgIf/Vg10 - Jg1.1/2.1/1.3/2.3) at 211, 220 bp. Immunoglobulin heavy chain (IgH) rearrangement: primer set A (FR1-JH): monoclonal peak at 347 bp, primer set B (FR2-JH): monoclonal peak at 252 bp, C (FR3-JH): monoclonal peak at 115 bp.

Proposed Diagnosis

-

Interesting Feature(s)

-

EA4HP24-LYWS-293

An indolent EBV-related clonal T-cell proliferation presenting as chronic rhinosinusitis

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Case Description

A 32-yo female had suffered recurrent fever (up to 38.5 °C), persistent nasal obstruction and rhinorrhea since 2017. Medical history and physical examination were unremarkable. Autoimmune diseases were excluded after extensive rheumatological workup. Laboratory tests evidenced mild leukocytosis and slight increased ESR and CRP, concomitant with febrile episodes. Blood cultures and check-up for systemic infectious disease were negative, except for a documented EBV infection 4 years before with transient EBV viremia (anti-EA IgG elevation, EBV-DNA plasma levels 753 IU/mL). Occasional nasal swabs positive for bacterial infections were treated with antibiotics, with only short-term relief. Upper airways endoscopy showed edematous mucosa with easily bleeding ulcerations, covered by crusts. CT scans confirmed turbinate hypertrophy and obstruction of maxillary sinuses. FDG-F18 PET documented an intense uptake in nasal cavities and nasopharynx. In 2019 the patient underwent endoscopic sinus surgery in another Institution, with histological diagnosis of reactive lymphoid hyperplasia. Recurrence of symptoms led to additional biopsies of nasal cavities, taken at our Institution in July 2023.

Biopsy Fixation Details

10% neutral buffered formalin/24h.

Frozen Tissue Available

NA

Details of Microscopic Findings

Mucosal fragments with focal ulceration and dense lymphoid infiltrate in the subepithelium, with minimal epitheliotropism. Lymphoid cells displayed small-to-intermediate size, irregular nuclei with indented outline, clumped chromatin, non-prominent nucleoli and scant cytoplasm. Scattered larger cells were present. Reactive

polyclonal plasma cells and rare granulocytes were noted. Necrosis, angioinvasion or angiodestruction were not observed.

Immunophenotype

Lymphoid cells were positive for CD3, CD2, CD8, to a lesser extent for granzyme B, with partial loss for CD5 and CD7 and negative for CD20, CD4, CD30, CD56, CD38, MUM1, OCT-2, PD-1, CXCL13. Proliferative index was low (Ki67 5-10%). EBV in situ hybridization (EBER) was positive in almost all lymphoid cells. Plasma cells showed occasional IgG4 expression. Central pathology review of the biopsies taken in 2019 revealed overlapping histological and immunophenotypical features with present ones.

Cytogenetics

NA

Molecular Studies

PCR analysis disclosed a clonal population of the TCR-gamma gene on 2023 biopsies; the same analysis on 2019 biopsies was unreliable. Whole genome sequencing revealed a heterozygous variant in *RIPK1* gene: c.1729+1G>A, which has not previously been described in literature; in silico predictive data indicates it is likely pathogenic. Of note, *RIPK1* gene is associated to CRIA syndrome (autoinflammation with episodic fever and lymphadenopathy).

Proposed Diagnosis

EBV-related clonal T-cell proliferation of uncertain malignant potential.

Interesting Feature(s)

This is a rare case of EBV-related clonal T-cell proliferation with long-lasting indolent behavior and low-grade morphology. Differential diagnoses include extranodal NK/T-cell lymphoma nasal-type (ENKTL), indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (iT-LPD-GI) and chronic active EBV infection (CAEBV). iT-LPD-GI affects the digestive system and is EBV-negative. CAEBV diagnosis is largely clinical and characterized by high viral load in PB or tissues, recurrent/persistent infectious mononucleosis-like symptoms, absence of immunodeficiency. ENKTL is usually characterized by high grade morphology and unfavorable clinical behavior. Rare cases of ENKTLs with indolent course have been reported in literature (Devins K, Diagn Pathol, 2018); clinical follow-up is warranted.

EA4HP24-LYWS-296

Primary cutaneous marginal zone B-cell lymphoma/lymphoproliferative disorder (PCMZL)

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Case Description

The patient is an 83- year-old man presented with an isolated subcutaneous resistance in the caudal scrotal wall of the left hemiscrotum. The lesion is 4,5x4,1,5 cm in diameter. Excisional biopsy was taken.

Biopsy Fixation Details

4% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Intact epidermis. Diffuse and pronounced infiltrate in the underlying stroma of small lymphocytes with slight atypical morphology. Fragments of smooth muscles seen.

Immunophenotype

The lymphocytes express the B- cell markers CD20 and CD79a with positive expression of BCL2 and low proliferation measured by Ki-67. There is no expression of CD5, CD23, CyklinD1, SOX11, CD10, BCL6. Few small residues of reactive germinal centers could be identified with positive expression of CD10, BCL6 and negative expression of BCL2. Very sparse plasma cell population with CD138 expression.

Cytogenetics

Not done

Molecular Studies

PCR shows clonal B-cell population.

Proposed Diagnosis

Primary cutaneous marginal zone B-cell lymphoma/lymphoproliferative disorder (PCMZL)

Interesting Feature(s)

PCMZL is an indolent cutaneous B-cell lymphoma that has been described preferably in trunk, upper extremities, and head. However, primary involvement of scrotum is rare, and a differential diagnosis including a variety of reactive cutaneous lymphoid proliferations and other B-cell lymphomas that may primarily or secondarily involve the skin should be well investigated.

EA4HP24-LYWS-315

Indolent T-lymphoblastic proliferation associated with low grade follicular dendritic cell sarcoma and Castleman disease

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Case Description

A 35-year-old woman with no history of malignancy or autoimmune disorder presented with an isolated 7.5 x 5.0 x 4.0 cm left neck mass developing over a 6 month time period. She had no associated B symptoms. A positron emission tomography-computed tomography (PET-CT) showed increased FDG uptake within the neck mass but no other areas of FDG avidity. She underwent an excisional biopsy of the mass at another institution. At our institution, a complete blood count was within normal limits (WBC 8.2 K/uL, hemoglobin 12.9 gm/dL, platelet 231 K/uL), and a bone marrow biopsy was also performed.

Biopsy Fixation Details

Not available. Material received from another institution.

Frozen Tissue Available

Not available.

Details of Microscopic Findings

Histologic sections of the excisional biopsy showed three distinct morphologic patterns. One consisted of a diffuse proliferation of spindled cells with oval to irregular nuclei, open chromatin, small nucleoli and scant cytoplasm. Another consisted of aggregates of monotonous, mature appearing small lymphoid cells with round nuclei, condensed chromatin, variably prominent nucleoli and scant cytoplasm. There were no mitotic figures and no significant morphologic atypia. Finally, there were also occasional small follicles with depletion of germinal center lymphocytes some surrounded by co-centric rings of small lymphocytes with occasional penetrating sclerotic blood vessels. The bone marrow biopsy showed a cellular marrow (50%) with trilineage maturing hematopoiesis and no abnormal infiltrates.

Immunophenotype

The spindle cell proliferation was positive for CD4, CD21 (subset), CD35 (subset), CD45 (weak), CD68, CD163, clusterin, D2-40 (subset), fascin, and vimentin; it was negative for S100, CD1a, CD2, CD3, CD5, CD7, CD8, CD10, CD15, CD23, CD30, CD34, CD43, ALK1, BCL6, EBER, EMA, MUM1, PAX5, and TdT. The Ki-67 proliferation index was 5-10% in the spindle cell areas. The lymphoid aggregates were positive for CD1a, CD2, CD3, CD4, CD5, CD8, and TdT; they were negative for CD10, CD20, CD21, CD23, CD30, CD34, CD35, CD43, CD163, ALK1, BCL6, and PAX5. The Ki-67 proliferation index was approximately 90% in the aggregates. In situ hybridization for Epstein Barr virus encoded RNA (EBER) was negative. CD20 and PAX-5

stains highlighted reactive follicles. CD21 and CD23 stains highlighted preserved follicular dendritic cell meshwork in a similar distribution to the follicles. Kappa and lambda stains highlighted scattered polyclonal plasma cells.
Reported flow cytometry performed elsewhere on the mass showed no diagnostic abnormality.
Flow cytometry performed at our institution on the bone marrow showed no immunophenotypic aberrancies.

Cytogenetics

Cytogenetic studies performed on the bone marrow showed a normal female karyotype (46,XX[20]).

Molecular Studies

Reported T-cell receptor (TCR) beta, TCR gamma, and immunoglobulin gene rearrangement studies performed on the mass detected no clonal gene rearrangements.

Proposed Diagnosis

Follicular dendritic cell sarcoma, low-grade, associated with foci of hyaline vascular Castleman disease and indolent T-lymphoblastic proliferation.

Interesting Feature(s)

- Indolent TdT positive lymphoblastic proliferations (iT-LBP) reported in association with other conditions:
  - Hepatocellular carcinoma, acinic cell carcinoma, angioimmunoblastic T-cell lymphoma, Castleman disease and follicular dendritic cell sarcoma.
- Morphology and immunophenotype consistent with cortical thymocytes.
- Important to recognize these indolent, TdT positive T-lymphoblastic proliferations to avoid misdiagnosis and overtreatment as T-lymphoblastic lymphoma.

EA4HP24-LYWS-319

Isolated, Centroblast-Rich, BCL2-Negative, Lymphoid Follicle with Follicular Lymphoma-like Ki67 Staining Pattern and *BCL6* Gain associated with Dermatopathic Lymphadenitis: Is it an Intrafollicular Pediatric-Type Follicular Neoplasm?

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Case Description

12 years ago, a 17M presented to his pediatrician with a mass in his right upper inner thigh. No pruritis skin condition was present. He was referred to a general surgeon, who excised the mass, put it in 10% NBF and sent it to the pathology department. Grossly, the mass was composed of a tan-pink, firm, disc-shaped lymph node, measuring 2.5 cm x 1.7 cm x 0.4 cm,

with smooth external surface. The lymph node was serially sectioned & showed tan cut surfaces. After the diagnosis was made, whole-body PET/CT scan showed no other lymph node enlargement or a mass lesion. Follow-up physical examinations & whole-body PET/CT scans for 5 years (till 2017) did not show any lymph node enlargement or a mass lesion. Patient has lost to follow-up since 2018.

Biopsy Fixation Details

10% NBF

Frozen Tissue Available

No

Details of Microscopic Findings

LN has preserved architecture with reactive follicles & a single atypical follicle with predominance of centroblasts & no tingible-body macophages in the germinal center of this follicle. Areas of paracortical hyperplasia with melanophages are also seen.

Immunophenotype

Immunohistochemistry: Germinal center (GC) lymphocytes are positive for CD20, BC6 (~60% positive) and CD10 (60% positive) with follicular lymphoma (FL)-like Ki67 staining pattern. GC B lymphocytes are negative for BCL2 & positive for MUM1 only in about 20% cells (< 30% positivity is considered negative). Some of the cells in the germinal centers are CD3+/CD5+/BCL2+ small T cells. CD30, CD15 & Epithelial Membrane Antigen are negative in the atypical follicle.

Cytogenetics

Not done

Molecular Studies

FISH for *BCL2/IGH* Translocation: Negative

FISH for *BCL6* Rearrangement: 56% of nuclei showed 3-4 copies of the *BCL6* gene region.

FISH for *IRF4* Rearrangement: Negative

B-Cell Clonality and NGS Studies: Not enough tissue for these studies

Proposed Diagnosis

Isolated, Centroblast-Rich, BCL2-Negative, Lymphoid Follicle with Follicular Lymphoma-like Ki67 Staining Pattern and *BCL6* Gain in association with Dermatopathic Lymphadenitis: Is it an Intrafollicular Pediatric-Type Follicular Neoplasm?

Interesting Feature(s)

1. **Isolated, Centroblast-Rich, BCL2-Negative, Lymphoid Follicle:** Such isolated follicles were described in the literature 4 years after we had our case [*PLoS ONE 11(3):e0151735. doi:10.1371/journal.pone.0151735*].
2. **Follicular Lymphoma (FL)-Like Ki67 Staining Pattern and Extra *BCL6* Copies by FISH:** Could we be dealing with an intrafollicular neoplasia of pediatric-type? *BCL6*, *BCL2* or *IRF4* alteration was not detected in the tested cases of such isolated, centroblast-rich, follicles reported in the literature [*PLoS ONE 11(3):e0151735. doi:10.1371/journal.pone.0151735*].
3. **No Lymphoma Developed during 5-year Follow-up:** These isolated FL-like follicles create concern for lymphoma for the patient, the family & the physician resulting in a long surveillance, but these follicles could be indolent lymphoproliferations & may not

be of any clinical significance. Moreover, FLs that lack t(14;18) have good prognosis (*Int J Oncol. 2000;56:7-17*).

4. **High-Grade Morphology of the Follicle:** FLs with *BCL6* alterations are of high grade (3A or 3B) (*Am J Pathol. 2004;165:481-490; Mod Pathol. 2008;21:973-978*).
5. **Dermatopathic Lymphadenitis (**Paracortical Hyperplasia with Melanophages): Could chronic antigen stimulation in dermatopathic lymphadenitis (DL) be pathogenetically related to atypical centroblast-rich follicle development? FL in-situ and a small cell B-cell lymphoma have been reported in association with DL (*Cancer. 1990;66:302-312; Case Rep Pathol. Volume 2013 | Article ID 481937 | https://doi.org/10.1155/2013/481937*).

EA4HP24-LYWS-322

A Rare Case of Duodenal-Type Follicular Lymphoma Presenting as Small Bowel Obstruction

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Case Description

A 65-year-old male presented with acute abdominal pain, non-bloody emesis, and constipation. A CT scan revealed small bowel obstruction, prompting an exploratory laparotomy with partial small bowel resection. Intraoperatively, multiple sessile polyps were identified within the small bowel, histologically confirmed as follicular lymphoma, grade I. Several weeks later, the patient was transferred to our hospital, where an endoscopy was performed. Imaging studies (PET/CT) showed multiple hypermetabolic lymph nodes in abdomen and pelvis, and no splenomegaly.

Biopsy Fixation Details

Multiple fragments of soft tissue labeled as “duodenal polyps” submitted for formalin fixation and embedded in paraffin.

Frozen Tissue Available

No

Details of Microscopic Findings

Histologic sections showed several fragments of small bowel mucosa and submucosa involved by lymphoma with a follicular pattern (figures 1A and 1B). The lymphoma cells were predominantly small centrocytes with rare, scattered centroblasts (figures 1C and 1D). No sheets of large cells were identified.

Immunophenotype

Immunohistochemical studies revealed the lymphoma cells to be positive for CD20 (figure 2A), CD10 (figure 2C), BCL2 (figure 2D) and BCL6 (figure 2E). Ki-67 showed an overall proliferation rate of less than 10% in the lymphoma cells (figure 2F). CD21 highlighted

networks of follicular dendritic cells that were seen preferentially at the periphery of the neoplastic follicles (figure 2B).

Cytogenetics

FISH studies were performed in our institution and were positive for *IGH::BCL2* gene rearrangement in 68.5% of the cells.

Molecular Studies

Next generation sequencing was performed in our institution and showed the following somatic mutations: *CREBBP* (4308T>G, VAF =28%), *HVCN1* (425T>G, VAF=27%), *KMT2D* (5113A>T, VAF =27%).

Proposed Diagnosis

Duodenal-type follicular lymphoma

Interesting Feature(s)

Duodenal-type follicular lymphoma (DTFL) is a rare variant of follicular lymphoma primarily located in the second portion of the duodenum. While most cases are incidentally discovered in asymptomatic patients, a subset of patients may manifest gastrointestinal symptoms. In this case report, the patient presented with small bowel obstruction, which is an unusual presentation for DTFL with only rare cases being reported in the literature. Remarkably, this unusual clinical presentation did not correlate with higher-grade histologic features, atypical immunohistochemical results, or the absence of *IGH::BCL2* gene rearrangement.

Furthermore, this case highlights the presence of somatic mutations previously reported in follicular lymphoma, including those associated with DTFL, such as CREBBP, HVCN1, and KMT2D.

EA4HP24-LYWS-328

CD4/CD8 double negative indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract

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Case Description

A 16-year-old young man had a hemolytic anemia with heat and cold antibodies, diarrhea and stagnation of weight gain. The lymphoma screening (esophagogastroduodenoscopy and coloscopy) was suspicious for MALT-lymphoma. Next to the initial biopsies at diagnosis, additional biopsies were performed nine months later.

Biopsy Fixation Details

4% buffered formalin, paraffin embedding

Frozen Tissue Available

-

Details of Microscopic Findings

Colon biopsies with a dense lymphatic infiltrate, partly with a nodular configuration. The cells are small and show dense, mature chromatin. The epithelium of the crypts is inconspicuous without an increase of intraepithelial lymphocytes. There are no lymphoepithelial lesions.

9 months later further biopsies of the small intestine and the colon show the same infiltrates.

Immunophenotype

The T cells are positive for CD3 and TIA1, but double negative for CD4 and CD8, as well as negative for CD103 and CD56. CD5 and CD7 are weakly positive. The cells show in partial heterogeneous positivity for CD57, and negativity for EBER, TDT, CD34, CD1a, and CD117. The proliferation rate (Ki67) is low. The majority of cells are positive for the αβ T cell receptor.

Cytogenetics

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Molecular Studies

Clonality analysis:

First biopsy: Detection of a T cell clone in TCRB Tube A (261bp) (IdentiClone® TCRB Gene Clonality Assay (Invivoscribe)), in TCRG 2.0 (195bp) (IdentiClone® T Cell Receptor Gamma Gene Rearrangement Assay 2.0 (Invivoscribe)), and in Trainor primer set I (226bp) and primer set II (202bp).

The second biopsy showed the same clones (TCRB Tube A 263bp, TCRG 2.0 194bp) with a minimal shift of 1 to 2 base pairs (possibly technical). Additionally, a clone in TCRB Tube C (302bp) was found.

There was no evidence for a B cell clone in the IGH analysis (Biomed-2, FR 2 and 3 primer set).

NGS analysis:

performed on the first biopsy: no mutation in *RHOA*, *IDH2*, *PRKCB*, *STAT3* and *STAT5B* (hotspot regions), or in *ATM*, *BCOR*, *CARD11*, *CCR4*, *CD28*, *CTNNB1*, *DDX3X*, *DNMT3A*, *FYN*, *IRF4*, *JAK1*, *JAK3*, *KMT2D*, *PIK3CD*, *PLCG1*, *SETD2*, *TET2*, *TNFRSF1B*, *TP53*, *VAV1*, *CD58*, *GNA13*, *PTPN1* and *TNFAIP3* (coding DNA) (custom panel, Ion GeneStudio S5 Prime System, Thermo Fisher Scientific).

FACS analysis of pB, 22 months after the diagnosis:

52% of all T cells are double negative T cells with αβ phenotype.

Proposed Diagnosis

ICC 2022: indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract

WHO 2022: indolent T cell lymphoma of the gastrointestinal tract

CD3+/CD4-/CD8-/TIA1+/αβ phenotype

Interesting Feature(s)

Most cases of indolent clonal T cell lymphoproliferative disorder of the gastrointestinal tract are CD4+, less frequent CD8+, and sometimes CD4+/CD8+ or CD4-/CD8-, like in this case.

Middle aged patients are most often affected, but in our case, is a young patient (16 years). The young age and the double negativity of the infiltrating and circulating T cells prompted us to raise the diagnosis of an autoimmune lymphoproliferative syndrome (ALPS); however, there are no clinical parameters to support this diagnosis. The CD4+ cases harbour a *STAT3::JAK2* fusion in a subset and recurrent alterations are mutations in *STAT3, TET2, DNMT3A, KMT2D*; and *SOCS1* deletions. In our case we could confirm the clonality of the lesion, but without the presence of the common gene mutations. After steroid therapy the hemolytic anemia and the diarrhea stopped and the young man is doing well. In the last control, the patient was asymptomatic, despite the presence of the T cell infiltrate with the same phenotype in the last intestine biopsy as well as the double negative T cell population in the last peripheral blood analysis.

EA4HP24-LYWS-337

Indolent CD4+ T-cell lymphoma of the GI tract with nodal and medullary involvement

Dr. Léna Mescam[1], Dr. Florian Pesce[1], Dr. Diane Coso[1], Prof. Laurence De Leval[2], Prof. Luc Xerri[1]

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Case Description

Incidental discovery of a monoclonal gammapathy (IgA *K* : 1.1g/L) in a 40-year old man without significant medical history.

No clinical abnormality.

Chest-abdomen-pelvis CT revealed an enlarged mesenteric adenopathy (4 cm diameter).

This adenopathy was resected through coelioscopy.

Biopsy Fixation Details

Formalin 4%.

Frozen Tissue Available

No.

Details of Microscopic Findings

Complete effacement of the lymph node architecture by a diffuse and monomorphous lymphoid proliferation. The cell proliferation was composed by small lymphocytes with round or ovoid and regular nuclei, fine chromatin, indistinct nucleoli and scant or moderate cytoplasm.

There was no mitosis, nor necrosis. No residual germinal center was found.

A few plasma cells were present.

Immunophenotype

- Positivity of CD2, CD3, CD5, CD7, CD4, PD1, TCRbF1

- Negativity of CD20, CD8, CD56, CD30, CD1a, TdT, CD10, BCL6, ICOS, CXCL13, CD23, Tia1, granzyme B, ALK, IgG4, PDL1 and negativity of EBER
- Plasma cells are CD138+, without light chain restriction.
- Proliferation index : Ki67 <10%

Cytogenetics

No

Molecular Studies

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- Clonality analysis :
  - Clonal rearrangement of *TCRB* and *TCRG*
  - No *IGH* nor *IGK* clonal rearrangement
- NGS : Mutation *STAT3*exon 20 : c1840A>C

Proposed Diagnosis

Nodal mesenteric infiltration by an indolent CD4+ T-cell lymphoma.

Follow-up : following this diagnosis, fibroscopy was done and showed numerous polypoid gastric/duodeno-intestinal lesions with lymphangiectasy.

Digestive biopsies revealed the same small T-cell proliferation in the gastric and colonic mucosae, allowing the diagnosis of **indolent T-cell lymphoma of the gastro-intestinal tract.**

A **bone marrow infiltration** was also present : lymphocytosis 20% with phenotypically abnormal T-cells, showing the same clonal TCR rearrangement.

Since 2018, a « watch and wait » strategy has been applied and the patient has no clinical sign of disease (5 years of follow-up).

In 2020 and 2023, fibroscopy showed the same polypoid lesions and biopsies showed identical histo-phenotypic features of non destructive, indolent T-cell lymphoma with gastric, duodenal and colonic mucosal localization.

(NGS analysis is ongoing on the last 2023 biopsies, in search for additionnal mutations that could have appeared since 2018).

Interesting Feature(s)

- Atypical presentation : **nodal mesenteric** T cell lymphoproliferation revealing an indolent T-cell lymphoma of the GI tract.
- **Bone marrow** infiltration, uncommon in this setting
- Despite the extension outside the GI : **stable** disease without treatment, after **5 years of follow up**,- Strong **PD1** positivity, uncommon and confusing in the context of an initial lymph node involvement

EA4HP24-LYWS-340

An indolent extranodal NK/T cell lymphoma

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Case Description

A 44-year-old woman with a sore throat and enlarged cervical lymph nodes presented in Haematology department in August 2020. A biopsy of the submandibular lymph node was signed out as a chronic NK lymphoproliferative disease related to EBV infection. She has been examined by head and neck surgeon for the similar condition several times in a past few years in an outside Hospital: first in October 2017 a hollow in her palate was found and PET-CT showed an inhomogeneous process in the soft palate measuring 16x30x36 mm. Biopsy was performed. Control PET-CT from April of 2018 showed no signs of disease but PET-CT from April 2019 showed enlarged right submandibular gland and bilateral cervical lymph nodes.The patient was treated with methotrexate and thalidomide. In February of 2021 a core needle biopsy of a cervical lymph node showed histological and immunophenotipical features suggestive of an extranodal NK/T-cell lymphoma, nasal type but the clinical history was not consistent. The biopsy material was sent for a consultation and the diagnosis was confirmed. Samples from previous years (2017, 2018, 2020) were also reviewed and were also considered to be part of the same process.During March and April of 2021, she received two cycles of DDGP (cisplatin, dexamethasone, gemcitabine, and pegaspargase) regimen. The regression of the size of the lymph nodes was described by the control CT. During May and June of 2021, 3rd and 4th cycle of DDGP were carried out. In July of 2021 pathological metabolic activity was described by PET-CT with stronger intensity on the right and weaker intensity on the left side of the neck in the control interval. In August of 2021 autologous stem cell transplantation was performed after conditioning according to the BeEAM (bendamustine, etoposide, cytarabine, melphalan) protocol. The posttransplant course was complicated by febrility, radiologically verified neutropenic colitis and S. epidermidis sepsis.In October of 2021, she was hospitalized due to prolonged febrility under suspicion of sepsis during which mycosis of the sphenoid sinus was diagnosed. In 2022, radiotherapy of the right submandibular node and nasopharynx was performed. After the treatment, complete remission has been achieved. At the last check-up in January of 2024, the patient showed no signs of lymphoma.

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

no

Details of Microscopic Findings

Biopsy of cervical lymph node from 2020 revealed expanded paracortex filled with small to medium-sized lymphocytes some of which were of T-cell phenotype, the others were CD3 (cytoplasmic, low intensity), CD5, CD8 negative but positive for CD2, CD7, CD56, TIA1, granzyme B, perforin which is consistent with NK cell phenotype. NK cells were EBER positive.

Immunophenotype

CD2+, CD3c+, CD56+, TIA1+, granzyme B+, EBER+, CD30+, CD5-/+, CD4-, CD8-, CD7-, ALK1-. The described large NK cells showed high proliferative activity (Ki-67 60%)

Cytogenetics

no

Molecular Studies

no

Proposed Diagnosis

Extranodal NK/T cell lymphoma, an indolent type

Interesting Feature(s)

Extranodal NK/T-cell lymphoma is characterized by vascular damage and prominent necrosis, cytotoxic phenotype and association with Epstein-Barr virus as well as with aggressive clinical behaviour. Our patient had an indolent clinical course. First biopsy demonstrates proliferation of small CD56+ EBER+ NK cells with low proliferation rate. Subsequent biopsy reveals atypical large NK cells with high proliferation rate. Histological features are compatible with extranodal NK/T-cell lymphoma.

EA4HP24-LYWS-349

A Case of Indolent T-Cell Lymphoma of the Gastrointestinal Tract

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Case Description

A man in his third decade presented with intractable diarrhoea and weight loss in 2014 which was severe enough to require prolonged parenteral nutrition. A diagnosis of autoimmune enteropathy was made and the patient treated sequentially with azathioprine, infliximab, methotrexate and vedolixumab without improvement. There was no improvement with a gluten-free diet and anti-tissue transglutaminase antibodies were negative. Symptomatic improvement was achieved with treatment with high dose corticosteroids.

On review of the original histology in 2019 there was no evidence of autoimmune enteropathy and a diagnosis of Indolent T-cell lymphoma of the gastrointestinal tract (ITCL-GI) was made. MRI studies of the small bowel showed diffuse thickening with no discrete masses and no lymphadenopathy. Direct visualisation of the small bowel was normal.

Good symptomatic control of the diarrhoea has been achieved by continuation of high dose steroids (prednisolone 40mg daily equivalent). The use of steroid-sparing agents including mercaptopurine and ciclosporin has been unsuccessful. The prolonged use of high dose steroids has resulted in a diagnosis of osteoporosis and the patient has suffered a fragility fracture of a thoracic vertebra and required bilateral cataract removal.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

none

Details of Microscopic Findings

Sequential duodenal biopsies from 2014 to 2023 are available and show consistent features. The small bowel villous architecture is preserved with no more than minor blunting and no loss of glands. The lamina propria is expanded by a population of small, bland, mature appearing lymphocytes which show only minor epitheliotropism. Mitoses are rare and this is no necrosis. No high grade lymphoma is seen.

Immunophenotype

The lymphoid cells show a consistent phenotype (CD3+ CD8+ CD4-). Initial biopsies showed the lymphocytes to be CD56 negative but biopsies from 2023 has shown focal expression of CD56. The lymphocytes are negative for CD25, Granzyme B, Perforin TIA1 and CD10. Proliferation assessed by Ki67 is consistently low (1-2%).

Cytogenetics

Not performed

Molecular Studies

Clonal T cell receptor beta chain or gamma chain gene rearrangement is consistently detected.
Germline sequence using a panel designed for investigation of primary immunodeficiency disorders identified a heterozygous splice region variant in IRF8 and a heterozygous missense mutation in STAT5b of uncertain significance.
Sequencing of the small bowel is planned.

Proposed Diagnosis

Indolent T-cell lymphoma of the gastrointestinal tract (WHO HAEM5)
Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract (ICC)

Interesting Feature(s)

Whilst *indolent* in terms of disease progression, ITCL-GI can result in significant morbidity as demonstrated by the need for parenteral nutrition and side effects from prolonged high dose steroid use.
Mutations in the JAK-STAT pathway have been identified in T cell lymphomas of the GI tract. Whilst the germline mutation in STAT5b is of unknown significance its presence invites speculation that it may be causative in this case.
The development of CD56 expression in the most recent biopsies, associated with the more aggressive Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma, raises the possibility that this may represent the early stages of transformation to more aggressive disease.

EA4HP24-LYWS-351

Cutaneous Marginal Zone Lymphoma

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Case Description

A 71 years old female presented with a back mass of approximately 6 months duration which bothered her when she was sitting. No change in size noted over this time period. Other than elevated cholesterol, no significant history. Mass excised with overlying skin.

Biopsy Fixation Details

In 10% buffered formalin fixative.

Frozen Tissue Available

No tissue is submitted for frozen section.

Details of Microscopic Findings

H&E sections revealed intact skin with underling subcutaneous tissue with a dense proliferation of atypical small lymphoid cells with “monocytoid features” and scattered enlarged follicles containing small benign germinal centers.

Immunophenotype
The atypical lymphoid cells are positive for CD20, PAX5, CD43 (partial and weak), BCL2, and MIB1 highlights 10-15% of the cells. These cells are negative for CD5, CD10, CD21, CD23, BCL6 and CD3. CD21/CD23 mark the expanded FDC meshwork. CD10/BCL6 mark the small germinal centers which are negative for BCL2. T cells are positive for CD3/CD5
Cytogenetics
Interphase FISH study is positive for gain of MALT1/18q in 29.0% of nuclei, and negative for MALT1 gene rearrangement.
Molecular Studies
PCR studies for B-cell immunoglobulin heavy chain and kappa light chain gene rearrangements, and MYD33 L265P mutation are negative.

Proposed Diagnosis
Extranodal marginal zone lymphoma involving the subcutaneous tissue.
Interesting Feature(s)
The case is interesting as to its morphological features of present as a dense lymphoid mass in the subcutaneous tissue, gain of MALT1/18q, and negative B-cell gene rearrangement study.

EA4HP24-LYWS-358

Isolated indolent mantle cell lymphoma of the stomach

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Case Description
A 60-year-old male presented with unexplained right upper quadrant abdominal pain. Initial upper endoscopy showed gastritis and duodenitis. A follow up upper endoscopy 6 months later again showed gastritis, and multiple random gastric biopsies were performed.
Biopsy Fixation Details
Formalin
Frozen Tissue Available
None
Details of Microscopic Findings
Biopsies were taken from the antrum, incisura, and body of the stomach, which all showed chronic gastritis. *Helicobacter pylori* was detected by immunohistochemistry in all gastric biopsy specimens. The incisura biopsies included five pieces of gastric mucosa; one of the five incisura biopsies showed involvement of the lamina propria by a diffuse infiltrate

composed of small lymphocytes with condensed chromatin, indistinct nucleoli, and small amounts of cytoplasm. Mitotic figures were not seen.

Immunophenotype

The infiltrate was composed of CD19-positive, CD20-positive B cells that were positive for CD43 and BCL2 and negative for CD10. CD5 was difficult to interpret due to admixed background T cells, but CD5 was not definitively positive on the B cells. Immunostains highlighted a small reactive germinal center; germinal center B cells were positive for CD10 and negative for BCL2. A Cyclin D1 stain was positive in a subset of the lymphocytes surrounding and extending away from the reactive germinal center, while a SOX11 stain was negative. The Ki67 proliferative index was appropriately elevated in the germinal center and was otherwise low in the lymphoid infiltrate (5-10%).

Cytogenetics

FISH analysis was positive for a CCND1::IGH rearrangement in 23% of analyzed cells. FISH was negative for a BIRC3::MALT1 rearrangement.

Molecular Studies

None

Proposed Diagnosis

Isolated indolent mantle cell lymphoma of the stomach

Interesting Feature(s)

The immunophenotype of the infiltrate described here (SOX11-negative, without definitive CD5 expression), is consistent with indolent mantle cell lymphoma (iMCL), also known as leukemic, non-nodal mantle cell lymphoma, which was an isolated finding in one of multiple concurrently performed gastric and colonic biopsies. One month following the biopsy, a CBC showed an isolated absolute lymphocytosis of 4.6 K/uL, with no other abnormalities. However, peripheral blood flow cytometry showed polytypic B cells, which represented only 8% of lymphocytes. A PET scan showed no lymphadenopathy and no evidence of FDG-avid lymphoma. All subsequent CBCs over the next 22 months and repeat peripheral blood flow cytometry showed normal results, with no lymphocytosis and no evidence of lymphoma. Typically, iMCL involves the blood, bone marrow, and spleen. Classic mantle cell lymphoma commonly involves the gastrointestinal tract and other tissues; indeed, SOX11-mediated signaling in classic mantle cell lymphoma is thought to drive migration of lymphoma cells into tissues (PMID 28533307). However, SOX11-negative iMCL lacks this SOX11-mediated signaling, and involvement of the gastrointestinal tract by iMCL has been only rarely described (PMID 24352646). In this prior study, 3/13 patients with iMCL showed a follicular chronic gastritis associated with *Helicobacter pylori* infection, with Cyclin D1–positive cells in the mantle zones of the reactive follicles, similar to the findings presented here. However, all of the previously described patients also had peripheral blood involvement detected by flow cytometry. In contrast, the patient presented here showed isolated gastric involvement, and has remained without evidence of systemic disease for two years.

EA4HP24-LYWS-360

Epidermotropic primary cutaneous marginal zone lymphoma

Dr. Jiehao Zhou

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Case Description

A 72-year-old female presented skin lesions erupting following a venous ablation in 12/2021. She had approximately 35 spots initially and most of them spontaneous resolved. It was initially thought to be dermal hypersensitivity reaction. However, 4-5 scattered papules and patches persist on shoulder, chest, back and thigh. She denied B symptoms and weight loss.

CBC: Normal Hgb and WBC with borderline thrombocytopenia, 143 x 10(9)/L

She underwent skin biopsies of shoulder and thigh lesions in Feb 2022 and chest lesion in April 2022.

Biopsy Fixation Details

•The skin punch biopsy was fixed in 10% neutral buffered formalin for 18 hours.

Frozen Tissue Available

•N/A

Details of Microscopic Findings

The skin punch biopsy demonstrates a moderately dense lymphocytic infiltrate within the papillary dermis and surrounding superficial and mid dermal vessels. The lymphoid infiltrate extends into the epidermis and along the basal layer of epithelia. These atypical lymphocytes are variable in size with a subset shows enlarged nucleus and distinct nucleolus. However, large aggregates/sheet of large lymphoid cells are not identified. Plasma cells or plasmacytoid lymphocytes are not evident.

Immunophenotype

Neoplastic cells are positive for CD20 and BCL-2

Neoplastic cells are negative for CD3, CD5, CD10, BCL-6, MUM-1, Cyclin D1, CD30, EBER, IgG, IgM, IgD, IgA, kappa and lambda.

Cytogenetics

N/A

Molecular Studies

Immunoglobulin gene rearrangement study:

IgH: Clonal IgK: Clonal

Proposed Diagnosis

Primary cutaneous marginal zone lymphoma with epidermotropism.

Interesting Feature(s)

1. Our case is unique because it demonstrates epidermotropic infiltrating pattern. Most of primary cutaneous marginal lymphomas (PCMZL) are characterized by nodular or diffuse infiltration of neoplastic B cells predominantly involving the dermis and subcutis.

Epidermotropism, a common histologic feature of cutaneous T cell lymphoma, only rarely reported in PCMZL in the literatures. The common features of epidermotropic PCMZL include elderly male, widely disseminated patches and plaque-like skin rash and higher incidence of subsequent extracutaneous involvement. Magro C et al (2016) speculated that the aberrant expression of CXCR3 in neoplastic B cells, a chemokine receptor, is associated with epidermotropic pattern of PCMZL.

2. Our case is more unique compared to previously reported epidermotropic PCMZLs because of two observations: 1. Female patient; 2. No extracutaneous involvement after approximately 18-months follow-up.

It is of interest to know the CXCR3 expression pattern in the current case. However, we do not have capacity to perform this IHC stain. In addition, it will be informative if a comprehensive molecular study can be performed on the current case.

EA4HP24-LYWS-361

A case of nodal T-follicular helper cell lymphoma mimicking Castleman's disease, hyaline vascular type, with a highly indolent behaviour

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Case Description

The patient was a 63-year-old female who had a mass in her right groin for 3 months. Imaging examination revealed multiple enlarged lymph nodes in her right groin. Subsequently, all enlarged lymph nodes were removed. Castleman's disease, hyaline vascular type (HVCD) was diagnosed at a local hospital. The patient then visited our hospital for a consultation. Despite our diagnosis of nodal T-follicular helper cell (TFH) lymphoma, the patient did not receive any treatment and is alive with no evidence of disease at a follow-up of 73 months.

Biopsy Fixation Details

neutral formalin

Frozen Tissue Available

N/A

Details of Microscopic Findings

The surgically resected lymph node specimen showed a preserved architecture comprised of numerous scattered lymphoid follicles with regressive germinal centers (GCs) surrounded by expanded mantle zones; the interfollicular area contained large numbers of small lymphocytes and scattered immunoblasts. Proliferative vessels were also present in the paracortex, sometimes penetrating into the expanded mantle

zones. Atypical lymphoid cells suggestive of malignancy were not found in either the hyperplastic follicles or the paracortex.

Immunophenotype

CD20 staining revealed the presence of hyperplastic follicles. The mantle zone B cells expressed IgD. CD21 staining revealed dense, concentrically arranged and sparse follicular dendritic cell (FDC) networks in the regressive GCs and the expanded mantle zones, respectively. Clusters of CD3+ CD4+ T cells positive for PD1, ICOS, CD10 ,and Bcl6, and negative for CXCL13, were found within the expanded mantle zones.

Cytogenetics

Next-generation sequencing (NGS) analysis revealed mutations involving *TET2*, *RHOA*^{G17V}, *BARD1*, and *ATR*.

Molecular Studies

IgH(-), Igκ(-), IgL(-); TCRβ (+), TCRγ (-), TCRδ (-).

Proposed Diagnosis

Progressive transformation of germinal center-like follicular T-cell lymphoma (PTGC-like FTCL)

Interesting Feature(s)

First, to the diagnosis of this type of TFH lymphoma mimicking a benign lesion in which the architecture is preserved and the lymphoma cells cannot be identified by morphology, immunohistochemical staining revealing a marked increase in the number of CD4+ T cells expressing at least two TFH markers in the expanded mantle zones, usually forming small clusters with increased expression levels, is the most important and basic clue. However, it is also necessary to detect monoclonal T cells by polymerase chain reaction and nodal TFH-lymphoma-associated mutations by NGS.

Second, Our studies (unpunished) have demonstrated that PTGC-like FTCL has a progressive morphological spectrum, with an early morphological stage characterized by preserved follicles with hyperplastic GCs and expanded mantle zones; with progression, GCs may regress and eventually disappear. The case presented here probably represents the intermediate stage of progression of PTGC-like FTCL.

Third, the most remarkable feature of this case is that the patient remained asymptomatic after a follow-up of 73 months without treatment. Our study (unpublished) showed that PTGC-like FTCLs tend to have a less aggressive clinical course compared to AITL, with patients with localized adenopathy at presentation (Ann Arbor stage I) showing indolent clinical course, and a few of them achieving long-term disease-free survival after surgical removal of enlarged lymph nodes. The case presented here is such an example. Longitudinal and comprehensive studies with larger sample sizes are needed to clarify whether the case presented here represents a distinct entity with indolent biological behaviour.

EA4HP24-LYWS-378

Duodenal-type Follicular Lymphoma – typically an incidental discovery, & indolent....

Dr. Lynne Goh, Dr. Lai Mun Wang

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Case Description

51 year old man with history of Childs A cryptogenic liver cirrhosis presented to the emergency room for haematemesis & melaena. An oesophagogastroduodenoscopy (OGD) revealed oesophageal varices, a gastric ulcer & small nodules in the duodenum. PET & CT scans did not show systemic disease. The bone marrow biopsy was negative for lymphomatous involvement. He received 4 cycles of Rituximab & has been on 2 to 3 yearly follow-up with OGD & colonoscopy without disease progression or transformation. The latest duodenal (D3) biopsy (2023) was virtually unchanged from the index biopsy 13 years ago.

Biopsy Fixation Details

Neutral buffered formalin for 24-48 hours

Frozen Tissue Available

-

Details of Microscopic Findings

All the duodenal biopsies (2010 to 2023 at 2-3 yearly intervals) show expansion of the lamina propria including the villi by a nodular proliferation of small lymphocytes with irregular nuclei (centrocytes). The abnormal follicles are devoid of tingible body macrophages. No large atypical lymphoid cells are noted.

Immunophenotype

The abnormal follicles in the duodenal mucosa comprise CD20, CD10, BCL6, BCL2+ small to medium sized B lymphocytes, outlined by CD21+ follicular dendritic meshworks. Cyclin D1, CD5, CD23 are absent, excluding mantle & small lymphocytic lymphoma. The follicles exhibit a low proliferation index of 5-10% by Ki67.

Cytogenetics

-

Molecular Studies

-

Proposed Diagnosis

Duodenal-type follicular lymphoma (WHO 5e, ICC) [DFL]

Interesting Feature(s)

Patients with DFL are typically asymptomatic & the disease usually an incidental discovery during endoscopy for other indications (in this case, upper GI bleed from varices).

The protracted clinical course (over 13 years) without disease progression or transformation attest to the indolent behaviour of DFL & its excellent prognosis.

Exclusion of secondary involvement by systemic/ nodal FL is important to prevent over-treatment.

EA4HP24-LYWS-380

Indolent PTCL NOS with leukemic picture and skin involvement

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Case Description

A 32 year old male, admitted due to leg oedema after coming back from a trip to Turkey 2005. A control blood test revealed eosinophilia with WBC : 17,0 Eo: 11,3. Radiology showed no lymphadenopathy, no changes in lungs. Infection (incl. parasite infection) was excluded. Flow cytometry of the blood showed 78% T-cells with CD4/CD8 ratio 2.5. T-cells were positive för CD3, CD2, CD5 and CD7. 13% av cells i lymphocyte gate positive for CD56. 4% were CD8+/CD57+ and 9% were CD57+/CD4+. Majority of T-cells were positive for CD45RO but negative for CD45RA. B-cells were 1% and were polyclonal.

Bone marrow aspiration showed increased eosinophilia but no aberrant T-cell population.

Tha patient was diagnosed hypereosinophilic syndrom and treated with Nucala but without good response. After 10 years, a control bone marrow sample was obtained revealing 9.6% eosinophils and 24,1% lymphocytes. Blood smears showed 33,3% eosinophils and 29,8% lymphocytes. At that time point no flow cytometry was available.

The bone marrow was performed two years later (2017; blood status WBC 14 x 10^9/L, Neu 8 x 10^9/L, Eo 0,6 x 10^9/L). Bone marrow smears revealed 35% eosinophils in bone marrow smears and in blood and but no lymphocytosis. Flow cytometry of the bone marrow showed 23% T-cells, with 50% of T-cells showing aberrant immunophenotype CD5++ CD3- CD2+ CD4+, and background of ordinary CD3+, CD5+ T-cells with CD4/CD8 ratio 1,2. PCR analysis showed clonal rearrangement of TCRG and TCRB genes. Cytogenetics didn't show any aberrancies.

A diagnosis of lymphocytic HES was made. The yearly control 2017- 2020 showed leukemic picture with atypical T-cells in blood and bone marrow, eosinophilia and from 2020 skin engagement but never lymph node involvement. The diagnosis of PTCL NOS was made 2020. The patient suffered from itching, showed progression of skin lesions, leukemic blood picture, fever, and was treated with MTX, steroids, CHOEP (4 courses) in 2021 but without good effect .In 2022, the patient received treatment with BV-DHAP, followed by allogen stem cell transplantation in April 2023, reaching remission wth MRD 0,017% in BM in July 2023, 0,012% Dec 2023. In Jan 2024 MRD 0,008% (blood).

Biopsy Fixation Details

Formalin fixed tissue

Frozen Tissue Available

no

Details of Microscopic Findings

Skin biopsy showed the epidermis which was unremarkable and no epidermotropism was seen. The upper dermis showed mild infiltration by small and medium-sized lymphocytes with presence of a few atypical medium-sized lymphocytes with variations in size and presence of morphologic irregularities on the nuclear contours.

Immunophenotype

Lymphocytic infiltrates in the skin contained almost exclusively CD5+ T-lymphocytes, whereas almost no CD20+ B-cells were present. The atypical T-cells showed reduced expression of CD3 (partial loss) and aberrant loss of CD7 expression. The atypical T-cells were CD2+, CD4+, and CD8-. CD30 was positive in a subset of T-cells (10%). The tumor cell proliferation assessed by the Ki67 marker was approximately 20% in the T-cell population.

Cytogenetics

normal

Molecular Studies

No FIP1L1, PDGFRA/B or FGFR1, no BCR/ABL translocation was detected. No C-KIT mutation. PCR analysis of blood and skin showed the same results regarding a clonal rearrangement of TCRG and TCRB genes.

Proposed Diagnosis

Indolent PTCL NOS with leukemic picture and skin involvement

Interesting Feature(s)

Indolent course. Leukemic picture with skin manifestation after 10 years of disease course. No lymph node involvement.

EA4HP24-LYWS-386

CD123-negative, *BRAF*-negative Hairy Cell Leukemia

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The University of Texas MD Anderson Cancer Center, Hematopathology, Houston, USA

Case Description

A 71-year-old man diagnosed with a small mature B-cell neoplasm in 10/2023 at another institution and referred to our hospital for further management. A differential diagnosis of HCL or HCLv was considered elsewhere. Additionally, ~2 months before he was diagnosed with Rosai-Dorfman disease involving skin and had been observed. CT abdomen showed splenomegaly (17.1cm) without lymphadenopathy. A CBC at presentation to our center showed thrombocytopenia with normal WBC and RBC counts (WBC 7.3K/uL, Hb 16.0gm/dL, platelets 86K/uL). A differential count showed monocytopenia (4% monocytes with AMC 0.23 K/uL) and 24% circulating hairy cells. A bone marrow work-up was performed

Biopsy Fixation Details

Formalin (10%) for fixation and Formic acid (10%) for decalcification

Frozen Tissue Available

NA

Details of Microscopic Findings

The bone marrow aspirate smears showed increased small, mature lymphoid cells with scant to moderate cytoplasm and circumferential hairy projections. The bone marrow core biopsy specimen showed slightly hypercellular bone marrow (50%) with trilineage maturing hematopoiesis and an atypical lymphoid infiltrate

Immunophenotype

Flow cytometry immunophenotyping performed on bone marrow aspirate identified a monotypic B-cell population (5.8%) with following immunophenotype

Positive: CD11c (bright), CD19 (bright), CD20 (bright), CD22 (bright), CD25, CD38 (dec/partial), CD45, CD103, CD200, HLA-DR and kappa monoclonal

Negative: CD5, CD10, CD23, CD43 and CD123

Immunostains performed on the core biopsy showed the neoplastic cells were positive for CD20 (interstitial and intrasinusoidal), Annexin A1 and TBX21, and negative for cyclin D1 and BRAF V600ECytochemistry showed that the neoplastic cells were TRAP positive

Cytogenetics

Conventional cytogenetics performed on the bone marrow aspirate showed a normal male karyotype (46,XY[20])

Molecular Studies

An 81-gene NGS panel identified somatic mutations in *MAP2K1* (VAF 8%) and *CREBBP* (VAF 7%) genes. No *BRAF* mutation(s) were detected

Proposed Diagnosis

Hairy cell leukemia involving ~30% of marrow cellularity

Interesting Feature(s)

CD123 and *BRAF* co-negativity in this case triggered referral of this patient to our institution for appropriate diagnosis and management. The referred differential diagnosis was hairy cell leukemia versus HCL-variant?

Features in favor of HCL:

Typical clinical presentation with thrombocytopenia, monocytopenia, no leukocytosis and splenomegaly in an elderly patient

Characteristic cytomorphology of hairy cells in peripheral blood and bone marrow

TRAP positivity by cytochemistry

Positivity for Annexin A1 and bright CD200 expression

Features unusual in of HCL included:

CD123 was negative

No *BRAF* V600E mutation

Additional comments

CD123 is positive in almost all (99-100%) cases of HCL, however, very rare case of CD123 negative HCL patients have been described in the literature (*Case Rep Oncol* 2020; 13: 1430–1440)

HCL diagnosis can still be rendered by flow cytometry if the case meets other criteria as seen in this case (monoclonal B-cell population with bright expression of B-cell markers, positivity of only 3 out of 4 of the following markers is required (CD11c, CD25, CD103 and CD123) and in an appropriate clinical context
BRAF V600E mutation by NGS is positive in ~80% of HCL cases. *BRAF* wild type HCL patients can show *MAP2K1* mutations as seen in our case. These HCL cases are often associated with IGHV4-34 immunoglobulin variable heavy chain rearrangementPatient has shown good partial response s/p 2 months of cladribine therapy with <5% residual disease. He was started in 01/2024 with rituximab weekly for 8 weeks

EA4HP24-LYWS-373

Indolent Precursor B-cell Expansion in a Reactive Lymph Node: A Sheep in Wolf's Clothing

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Case Description
A 48-year-old female presented with shortness of breath.
CT Chest: Pulmonary edema. Bilateral axillary lymphadenopathy
Left axillary lymph node (LN) biopsy was performed.
Biopsy Fixation Details
Formalin
Frozen Tissue Available
NA
Details of Microscopic Findings
Reactive lymph node with intact architecture displaying both follicular and interfollicular hyperplasia, focal monocytoid B-cell hyperplasia, and nodular paracortical hyperplasia without any overtly atypical histologic findings.
Immunophenotype
Normal distribution of predominately follicular, as well as moderate numbers of interfollicular, CD20+ PAX5+ B-cells. CD10, in addition to highlighting germinal center B-cells, also reveals focally prominent perisinusoidal CD10+ cells that account for ~10% of cellularity. These extrafollicular CD10+ cells are CD20+ PAX5+ B-cells, a subset of which are positive for Tdt but negative for BCL6, thus representing early B-cell precursors that are predominately perisinusoidal. These cells are morphologically difficult to distinguish from mature lymphocytes.

Cytogenetics

NA

Molecular Studies

IGH PCR

Polyclonal

TRG PCR

Polyclonal

NGS

No disease associated variants

Two variants of uncertain significance (VUS)

BRCA2 49% VAF

CREBBP 48% VAF

VUSs are interpreted to be inconsequential germline SNPs

Proposed Diagnosis

Reactive lymph node with an expansion of precursor B-cells.

Note

Negative IGH and NGS indirectly support the impression that the expansion of precursor B-cells is likely to be non-neoplastic, but minimal involvement by a precursor B-cell neoplasm that is more overtly manifest elsewhere still cannot be excluded with certainty.

Interesting Feature(s)

- **Physiologic B-cell precursor (hematogone) hyperplasia** occurs in the **bone marrow (BM) or blood** in a variety of reactive conditions, particularly in children recovering from chemotherapy, aplastic conditions, other forms of bone marrow injury, and viral infections. The morphological and immunophenotypic features of hematogones require a careful differential diagnosis to rule out B-lymphoblastic leukemia (B-ALL/LBL).
- **Nodal expansions of physiologic T-cell precursors(iT-LBP)** are well described, but similar nodal expansions of B-cell precursors have not been well documented.
- Our case is an example of **nodal precursor B-cell expansion in a reactive LN (iB-LBP)**. They appear to be morphologically innocuous and were identified by chance on routine IHCs that were performed due to lack of tandem flow cytometry.
- iT-LBP typically form tumor-like masses in a paracortical and interfollicular distribution; iB-LBP in our case did not form a mass lesion and predominate multifocally near medullary sinuses.
- Polyclonal IGH PCR and negative sequencing in our case suggests that these are non-clonal proliferations (noting their relatively low frequency that may be below the level of detection). After years of follow-up, patient has not developed a B-ALL/LBL, suggesting that these are truly indolent expansions akin to iT-LBP.
- We (Lee W et al. USCAP, Hematopathology, 1413 Mod Pathol. 2020) and others (Stone A et al. Am J Clin Pathol. 2022) have **recently identified sizeable expansions of precursor B-cells in reactive LNs.** Flow cytometry was helpful in some cases showing the characteristic maturation immunophenotypic pattern of hematogones.

- Our case highlights that **recognition of these populations is important to avoid misdiagnosis** of low-level B-LBL or light chain negative CD10+ B-cell lymphoma (when detected by flow). While these precursor B-cell expansions in a reactive LN are typically benign, additional workup such as molecular studies might be recommended to rule out underlying neoplasm.

EA4HP24-LYWS-376

Classifying an epiglotic lymphoid T proliferation

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Case Description

In March 2023, during intubation, is discovered in a 67 year old man, hospitalized for inguinal hernia surgery,a swollen epiglottis. Swallowing problems for 6 months, with dry cough, without change in general condition is evidenced, with a story of cutaneous lesions. Peripheral thrombopenia is evidenced.

In 2014, a right calf lesion is described as epidermal hyperplasia associated with angiogenesis. In 2017, cutaneous lesion is getting worse in a context of polyadenopathy with a necrotic form on the posterior surface of the right leg and right ankle, and erythematous-purple macule. New biopsies shows capillary necrosis, strongly expressing PD1 cytologically irregular dermal lymphocytic infiltrate.In lymph node, no hemopathy is visible; with T immunophenotyping highlighting a majority monoclonal T population in nodal and cutaneous biopsies. Conclusion raises the possibilities of lymphocytic macular arteritis/periarteritis nodosa with lymphoproliferation or PD1-expressing T-cell lymphoma, including cutaneous localization secondary to angioimmunoblastic or related T-cell lymphoma. Corticosteroids treatment is started with symptoms disappearance. In 2018, vasculitis exhibits persistent remission, under 5 mg of Prednisone, but inguinal and axillary enlarged lymphe nodes are still visible.

In 2022, a flare-up of vasculitis, in the form of a non-ulcerated lesion of the right upper thigh and ulcerations of the right ankle, regress under Cortancyl 40mg.

CT Scann, cervico-facial MRI : thickened appearance of the epiglottic region without sign of locoregional invasion. Small cervical lymphadenopathy.

PET-CT: 1. No suspicious hypermetabolism of the epiglottis or valleculae.

2. Several supra- and subdiaphragmatic lymph node formations infracentimetric and weakly to moderately hypermetabolic associated with homogeneous splenomegaly.

Biopsy Fixation Details

4% buffered formalin

Frozen Tissue Available

None

Details of Microscopic Findings

Epiglotic chorion is entirely occupied by an abundant monotonous lymphoid infiltrate of diffuse architecture, composed of small lymphocytes, with clear cytoplasm, convoluted nucleus, dense chromatin and marked nuclear membrane, accompanied by an inflammatory background made up of plasma cells, rare polynuclear eosinophils and quite numerous histiocytes sometimes with an epithelioid appearance grouping together in small clusters. There is epitheliotropism with numerous lymphoid cells in exocytosis. Absence of large cell range. Absence of necrosis

Immunophenotype

Lymphoid infiltrate is mainly composed of CD5+, CD2+, CD3+, CD4+, CD7-, CD8-, CD56-, GATA3-, ALK1- T cells. The cytotoxicity markers Granzyme B, Perforin, TiA1, are mainly negative with a few scattered immunolabeled elements. TFH markers are negative (CD10-, CXCL13-, BCL6-, faint and variable ICOS, PD1-).

CD20 marks a few scattered B elements. CD30 marks rare activated immunoblastic cells. No expression of KIR3DL2.CD23 does not reveal a follicular dendritic network. The histiocytes are CD68+ accompanied by some PS100+, CD1a+/- elements. No expression of KIR3DL2.

The proliferation index assessed using Ki67 is low, less then 5%.

EBER in situ hybridization looking for EBV cells is negative.

Cytogenetics

None

Molecular Studies

2017: monoclonal T population. No RHOA or IDH2 mutation in kin and lymph node.

2023: Majority monoclonal T population.

Targeted NGS reveals no mutation.

Proposed Diagnosis

Indolent T-cell lymphoma of the gastrointestinal tract

Interesting Feature(s)

Clinical history of cutaneous lesions with no without phenotypic link with the epiglotic lesion

Follow up: monitoring with stable clinical condition

Larynx location

EA4HP24-LYWS-396

Primary duodenal type follicular lymphoma

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Case Description

•44 year old gentleman presented with dyspepsia for over 2 months.
•The patient was prescribed Anti H. pylori treatment but there was no relief.
•He gradually developed loss of appetite over next two months.
•An upper GI endoscopy was performed and a duodenal (peri-ampullary) thickening extending to the third part of duodenum was seen and biopsy was taken which was reported as lympho-proliferative disorder by a community hospital.
•The patient was referred to Tata Memorial Hospital. PET CT was performed along with repeat biopsy.
•FDG avid wall thickening noted involving the duodenum, with maximum wall thickness of 2cm, SUVmax 21.77.
•FDG avid wall thickening noted involving the jejunum, with maximum wall thickness of 2.3cm, SUVmax 10.90.
•FDG avid epiphrenic nodes noted, largest measuring 2.2cm, SUVmax 5.71.
•Marrow appears unremarkable.
•Liver and spleen appear unremarkable.

Biopsy Fixation Details

•10% neutral buffer formalin for 8 hours.

Frozen Tissue Available

No

Details of Microscopic Findings

•The biopsy shows duodenal mucosal fragments with dense infiltration sheets of intermediate sized atypical lymphoid cells in lamina propria and all villi.
•There is no evidence of any high grade areas in this biopsy.
•These lymphoid cells also show plasmacytic cytomorphology at places.

Immunophenotype

These lymphoid cells are diffusely positive for CD20, CD10, BCL2 and CD138 (weak); negative for CyclinD1 and CD23.
•MIB-1 labelling index is 10-15%.

Cytogenetics

Not done

Molecular Studies

Not done

Proposed Diagnosis

Primary duodenal follicular lymphoma.

Interesting Feature(s)

Rare

Plasmacytic differetniation.

EA4HP24-LYWS-404

Duodenal-type follicular lymphoma, a classic case that never goes out of style

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Case Description

A 60-year-old female, with a personal history of neurological comorbidities due to a Poliomavirus infection as a child, complained with gastroesophageal reflux. She had no other symptom. Physical examination was unremarkable. Gastric endoscopy showed a duodenal atypical granular laterally spreading tumor, developed on the hemicircumference around the papilla. A biopsy was performed. CT-scan showed no tumoral syndrom. Patient was then lost to follow up.

Biopsy Fixation Details

Neutral buffered formalin was used for 24h.

Frozen Tissue Available

No

Details of Microscopic Findings

There were no epithelial abnormalities: normal enterocyte height, no intraepithelial lymphocytes increase, no dysplastic lesion. Villosities had an enlarged axis. A lymphoid nodular proliferation was found in the mucosa. The nodules were made of a homogenous lymphoid cellular population, without histiocytes or a mantle zone circling them. Tumor cells were small or middle-sized lymphocytes showing angulated, elongated, twisted, or cleaved nuclei, corresponding to centrocytes. A few scattered centroblasts were seen, never set in a diffuse growth pattern. Tumor cells were also found outside of the nodules and in the enlarged villosities' axis.

Immunophenotype

Tumor cells had a B cell lineage (by immunohistochemistry): CD20(+), CD5(-), CD10(+), BCL6(+), BCL2(+), CD30(-). CD23 antibody showed a dissociated and aside pushed follicular dendritic cells meshwork, inside the nodules.

Cytogenetics

None

Molecular Studies

None

Proposed Diagnosis

Duodenal-type follicular lymphoma (OMS 2022/ ICC 2022)

Interesting Feature(s)

This case illustrates the typical story leading to this diagnosis. Patients are usually asymptomatic and have their endoscopic exam for symptoms that are not linked to that lesion. The lesions seen by endoscopists were as described in the books: scattered whitish granular lesions, small nodules. Then, pathology exam showed nothing more but the morphology and immunophenotype wanted for this diagnosis. In this variant of follicular lymphoma, disease course is most commonly indolent. Therefore, treatment strategies vary from a wait-and-watch strategy to monotherapy treatment by Rituximab and/ or radiotherapy.

In the end, this is a classic case and classics, never go out of style.

EA4HP24-LYWS-408

Clonal T-cell lymphoid infiltrate with TFH phenotype

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Case Description

A 52-year-old man born in Guinea Ecuatorial, with a history of thalassemia minor, mild neutropenia, and epilepsy, presented with pruritic lesions in May 2022. Physical examination showed multiple papules involving the trunk and chest (1st biopsy). The lesions appeared in 2020 and extended progressively to the neck, axillary and inguinal areas, and anterior side of the arms. The legs were not involved. The patient did not report B symptoms; CT-scan studies did not identify lymphadenopathies or hepatosplenomegaly; only mild enlargement of the anterior mediastinal fat was observed, and reported as thymus hyperplasia. The lesions were recurrent and persistent despite steroid treatment. Two additional biopsies were performed (2nd biopsy, October 2022; 3rd biopsy, Jan 2024).

Biopsy Fixation Details

4% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

All three biopsies had similar features and showed nodular and perivascular lymphoid aggregates of lymphoid cells, non-epidermotropic, mostly located in the superficial dermis. The infiltrate was composed of small to medium-sized cells, admixed with scattered large cells with irregular nuclei, evident nucleoli, and scant cytoplasm.

Immunophenotype

Same immunophenotype occurred in the three biopsies. The aggregates were composed by polytypic CD20 positive cells. In the periphery of B-cells there were groups of atypical

cells positive for CD3, CD5, CD4, PD1, CXCL13, BCL6, CD10, GATA 3 and beta-F1, with loss of CD7 expression. Few cells expressed CD30. EBV was negative (EBER negative) in all biopsies. T-bet, CD56 and cytotoxic markers (TIA-1, granzyme B) were also negative. Ki-67 was moderate in the second biopsy and lower in 2024 biopsy.
Peripheral blood flow cytometry performed in July 2022, did not show abnormal CD3s-CD4 positive circulating cells. There were no circulating atypical cells, by flow and morphology. However, same clonal spikes in blood and both 2022 biopsies were observed. New peripheral blood samples have been asked.

Cytogenetics

No

Molecular Studies

Comparative TCR gamma and beta PCR was performed in the first two samples, showing the same clonal population in both. Studies in the biopsy performed in January 2024 are ongoing.
NGS not performed.

Proposed Diagnosis

Atypical T cell lymphoid infiltrate with TFH phenotype (with uncertain biological behavior).

Interesting Feature(s)

This case represents an indolent clonal T/TFH atypical cutaneous persistent lymphoid proliferation without evident systemic involvement after 4 years. Maybe it represents an indolent TFH proliferation, an indolent cutaneous phase of AITL or a true primary cutaneous TFH lymphoma (JY Wang, Am J Dermatopathol 2017). This is a clinical situation that exists and the biological behavior is uncertain, indicating careful follow-up in this setting.

EA4HP24-LYWS-407

Leukemic Non-Nodal Mantle Cell Lymphoma of the Eye with Plasmacytic Differentation.

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Case Description

A 73-year-old patient, who had previously undergone bilateral cataract surgery, presented a pigmented lesion in the ciliary body during a follow-up visit for choroidal detachment in the left eye.
Wide-field retinography revealed a pigmented, multilobulated intraocular lesion at the inferior temporal level, further confirmed by ultrasound characteristics as suspicious for melanoma. Accordingly, ocular enucleation was performed. Macroscopically, a distinct

whitish, polylobulated nodular lesion was noted in the inferior pole, within the region of the ciliary body and the choroid.

Biopsy Fixation Details

Formalin-fixed (10% neutral buffered formalin), paraffin embedded.

Frozen Tissue Available

Yes.

Details of Microscopic Findings

Infiltration by a monotonous lymphoid proliferation composed of medium-sized lymphocytes, with areas of clear cytoplasm – monocytoid-like in appearance , slightly irregular nuclei and mature chromatine. Sparse cells with abundant cytoplasm, cytoplasm lateralized nuclei, and presence of Dutcher bodies stood out.

Immunophenotype

Positive markers: CD20, CD79a, PAX5, MUM1, CD21, CD5, Cyclin D1, Kappa light chain restriction.

Negative markers: SOX11, CD10, p53.

Proliferation index (ki67): 30%.

Cytogenetics

Flow cytometry: two clones identified: a predominant clone of red-labeled B lymphocytes (CD5/CD23 positive and CD200/CD10 negative), and a minor clone of only 2%, with CD200 positivity and an immunophenotype consistent with CLL.

Molecular Studies

Pyrosequencing: MYD88 L265P mutation not detected.

FISH CCND1/IGH: detected the t(11;14) translocation in 60% of cells

NGS: - IGHV mutated (92.63% identity).

- IGH rearrangement: IGHJ4 - IGHD3-10 - IGHV4-34.
- t(11;14) positive.
- MYD88 S219C mutation.

Proposed Diagnosis

Leukemic Non-Nodal Mantle Cell Lymphoma with Plasmacytic Differentation.

Interesting Feature(s)

- There are no previous reports on ocular presentation of leukemic non-nodal mantle cell lymphoma with plasmacytic differentiation

- To date, few cases of MYD88 mutated non-nodal mantle cell lymphomas with plasmacytic differentiation have been described.

- Mantle cell lymphomas with plasmacytic differentiation and MYD88 mutation are very rare. Until now, only 3 cases have been reported in the literature, all of them harbouring the t(11;14) and with significant presence of Dutcher bodies. Remarkably, NGS studies performed in our case disclosed a MYD88 S219C mutation, which differs from the more typical L265P described in the other cases.

EA4HP24-LYWS-419

Marked erythrophagocytosis in a patient with primary cold agglutinin disease

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Case Description

The patient is an 82-year-old woman with a history of heart failure and hemolytic anemia. She was admitted with nausea and diarrhea due to infectious gastroenteritis. Her course was complicated by pneumonia, volume overload, and hemolytic anemia requiring blood transfusions. Blood cultures and a respiratory virus PCR panel were negative. CT showed nodular and ground glass pulmonary opacities, concerning for fungal or mycobacterial infection. CT also identified mildly prominent mediastinal lymph nodes, favored reactive secondary to pneumonia. No pronounced lymphadenopathy or splenomegaly. An automated CBC with differential was flagged for red cell and platelet abnormalities (MCV, MCH, and MCHC markedly elevated, PLT count unable to report due to clumping). After blood dilution in warm saline, MCV, MCH, and MCHC all returned to normal range. PLT count was still unreportable. Additional laboratory evaluation was notable for increased LDH, reduced haptoglobin, marked cold agglutinin titer (1:10240) with evidence of a cold autoantibody with I specificity, and serum immunofixation with a faint IgM-kappa monoclonal gammopathy.

A peripheral blood smear review and flow cytometry were ordered. Shortly thereafter, the patient declined any additional evaluation/intervention and was discharged to hospice.

Biopsy Fixation Details

Not applicable. Peripheral smear only.

Frozen Tissue Available

No.

Details of Microscopic Findings

Peripheral blood: Normocytic anemia with red cell agglutination and occasional spherocytes. Monocytes are increased with frequent erythrophagocytosis. Granulocytes and lymphocytes are unremarkable. Platelets show marked clumping.

Immunophenotype

Flow cytometry reveals a small monotypic B-cell population (0.4%), which is CD5(partial dim+), CD10(-), CD19(+), CD20(+), CD22(+), CD23(-), CD103(-), CD25(-), CD38(+), kappa surface light chain(dim+), lambda surface light chain(-). Monocytes carry a normal immunophenotype.

Cytogenetics

Not performed.

Molecular Studies

Not performed.

Proposed Diagnosis

Cold agglutinin disease (WHO 5th edition online beta version) / Primary cold agglutinin disease (International Consensus Classification 2022), with markederythrophagocytosis.

Interesting Feature(s)

- Markedly abnormal red cell indices should prompt peripheral smear review. Artifact due to cold agglutinins can be ameliorated by dilution in warm saline or other warming methods.
- Cold agglutinins can be primary (i.e. due to an underlying low-grade lymphoproliferative disorder that does not meet criteria for overt lymphoma) or secondary (due to lymphoma or infectious, inflammatory, or autoimmune disorders).
- Erythrophagocytosis is an uncommon morphologic abnormality that should prompt additional evaluation for viral and mycoplasma infections, hematologic malignancies (including monocytic leukemias) and autoimmune hemolysis (warm and cold autoimmune hemolytic anemias, paroxysmal cold hemoglobinuria, and cold agglutinin disease).
- It is unclear whether the patient's concomitant gastroenteritis and pneumonia contributed to an acute exacerbation of her cold agglutinin disease.

EA4HP24-LYWS-420

An isolated pulmonary nodule: a serious illness?

PhD/MD Pascale Cervera[1,2], Dr. Romain Heritier[1], Dr. Lucian Craciun[1], Dr. Adrien Pecriaux[1], Dr. Denis Debrosse[3], Dr. Marine Armand[2]

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Case Description

Discovery during a CT scan of a 13 mm right upper lobar pulmonary nodule in ground glass, mixed, slightly dense, non-hypermetabolic in a 68 year old man.
Antibiotic therapy with AUGMENTIN does not lead to regression.- PET scanner :
No suspicious hypermetabolic focus of the mediastino-hilar, cardio-phrenic lymph node areas.
No pathological pleural hypermetabolic focus. No pleural or pericardial fluid effusion.
Calcified nodules measuring 5 mm in the right upper lobe and 4 mm in the lateral segment of the middle lobe, non-hypermetabolic, with a quiescent appearance.
- Background
HTA.
Non-insulin requiring type 2 diabetes.
1998 and 2012:

Recurrent phlebitis under Rivaroxaban.
Several thromboembolic episodes with pulmonary embolism
Facteur II mutation
2021: COVID vaccination
Right upper lobectomie was performed

Biopsy Fixation Details

4% buffered formalin

Frozen Tissue Available

None

Details of Microscopic Findings

- The 0,9 cm parenchymal nodule corresponds to an interstitial lympho-plasmacytic infiltrate of low to moderate intensity, with patches of regular mature lymphocytes and plasma cells, concentrating in primary lymphoid nodules, without obvious germinal center. It enlarges the alveolar septa, without parenchymal destruction, nor lympho-epithelial lesion. it is centered by a fibrous pauci-cellular scar.
  - The lymphocytes are regular, rounded, small and the plasma cells are mature.
  - The alveoli are lined with regular pneumocytes
    - No necrosis.
    - Lack of large cell range
    - Absence of amyloid deposit

Immunophenotype

- The lymphoid infiltrate is made up of primary lymphoid follicles, distributed regularly, of small CD20+, Bcl2+, Bcl6- and CD10- lymphocytes.
  - They are surrounded by small CD3+ and CD5+ T lymphocytes.
  - Between these lymphoid follicles, the B and T lymphoid infiltrate which thickens the septa is of moderate density.
  - CD23 highlights a well-defined network of follicular dendritic cells at the level of lymphoid follicles.
  - Mature plasma cells are highlighted by CD138.
    - In situ hybridization of the Kappa and Lambda light chains, shows an imbalance of expression in favor of the Lambda light chain.
    - Exceptional IgG4 plasma cells.
  - The Ki67 proliferation index is low (5% maximum).
    - TTF1 underlines reactive pneumocyte hyperplasia; pancytokeratin AE1/3 underlines the absence of lymphoepithelial lesion.

Cytogenetics

None

Molecular Studies

B clonality : a minority clone B on the heavy and light chains is evidenced.
·T(11;18)q21 n situ hybridization: no rearrangement
·NGS in progress

Proposed Diagnosis

Lymphoid hyperplasia nodule, with minimal B clone

- very well limited, with complete excision
- without any sign of aggressiveness : no lymphoepithelial lesion, moderate lymphocyte density, low Ki67
- suspicion of association with a minimal MALT marginal zone small B-cell lymphoma

Interesting Feature(s)

Lymphoid hyperplasia nodule, with minimal B clone

- very well limited, with complete excision
- without any sign of aggressiveness : no lymphoepithelial lesion, moderate lymphocyte density, low Ki67
- suspicion of association with a minimal MALT marginal zone small B-cell lymphoma

EA4HP24-LYWS-423

Indolent follicular lymphoma of parotid gland in a patient with melanoma and clonal local plasma cell proliferation associated with Talimogene laherparepvec infusion for metastatic melanoma

Dr. Mihai Merzianu

Roswell Park Comprehensive Cancer Center, Department of Pathology, Buffalo, USA

Case Description

The patient is a 96-year-old man diagnosed in 2005 with malignant melanoma of the left calf initially excised with clear margins and negative sentinel lymph node. In 2011, in-transit melanoma occurred followed by multiple locoregional recurrences over the years, but without distant spread. These have been treated with multiple excisions, left leg isolated limb infusion, and dabrafenib/trametinib. Eight weeks after intralesional talimogene laherparepvec (T-VEC) infussion in 2020, a biopsy was performed to assess residual disease. In 2013, a staging PET scan showed no evidence of metastatic melanoma but identified an avid focus in the parotid gland which was diagnosed as follicular lymphoma on fine needle aspiration. The parotid nodule was not treated but has remained stable between 2013 and 2023 with slight increase from 1.6 cm to 2.3 cm diameter.

Biopsy Fixation Details

Formalin-fixed, paraffin-embedded tissue

Frozen Tissue Available

No

Details of Microscopic Findings

Core needle biopsy of parotid nodule in 2019 showed a dense lymphoid infiltrate without plasma cell differentiation, neoplastic follicles comprising numerous centroblasts (grade 3a). Tumor involved salivary gland parenchyma.

Several previous skin biopsies of recurrent melanoma from 2011, 2013, 2020 and 2021 were reviewed. None showed local inflammatory response. The punch biopsy at the T-VEC injection site revealed scattered lymphocytes and sheets of plasma cells involving the dermis and subcutis. Plasma cells exhibited mild nuclear pleomorphism with hyperchromasia and numerous immunoglobulin eosinophilic crystals but no prominent nucleoli or Dutcher bodies. Rare giant cells, frequent T cells and sparse B cells were seen. No germinal centers were identified. Patchy necrosis was present, but no viable melanoma cells were seen.

Immunophenotype

Parotid: follicular lymphoma cells expressed CD10, CD20, CD23, BCL2 (weak) and BCL6. Only sparse polytypic plasma cells were present around the tumor.

Skin: plasma cells expressed CD138, kappa, MUM1, CD19 (subset), and were negative for CD3, CD5, CD10, CD21, CD56, BCL-1, CD117 and lambda. B cells were rare and most admixed lymphocytes were T cells. SOX10 was negative for residual melanoma.

Cytogenetics

Not performed

Molecular Studies

Follicular lymphoma (2019): clonal rearrangement of IgH FR1 (314 bp) and negative IgK

Plasma cells post T-VEC: clonal rearrangements of IgH FR1 (323 bp), IgH FR3 (96 bp) and IgK (tube A:196 bp, tube B: 282 bp)

Proposed Diagnosis

Follicular lymphoma with minimal progression during a decade

Clonally unrelated monotypic plasma cell infiltrate post T-VEC infiltration for recurrent melanoma

Interesting Feature(s)

1. Two unrelated and incidental clonal disorders in same patient, both untreated without progression
2. T-VEC is a novel oncolytic viral immunotherapy derived from herpes simplex virus type 1, genetically modified to stimulate antitumor immune response
3. Several cases of local granulomatous inflammation and melanosis were reported but only three cases of plasma cell proliferation at TVEC infiltration site, two of which were clonal

EA4HP24-LYWS-427

Paediatric-type follicular lymphoma, case report uncommon

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Case Description

Pediatric follicular lymphoma (PTFL) is an uncommon entity that usually affects young population. Despite its high-grade histopathological characteristics, it presents lymph node involvement and the course is indolent. This case presents in an unusual age range, being a challenging pathological diagnosis.

A 47-year-old male patient with no personal or family medical history of interest presented with a three-year history of a right cervical slow growth lymphadenopathy. Physical examination revealed a painless, mobile nodule measuring 18 x 10 mm in the right cervical region, with no evidence of organomegaly or abnormalities in cardiopulmonary examination. Biochemical parameters were within normal ranges, the pathological examination confirmed a Pediatrics-type follicular lymphoma (PTFL). Since the diagnosis, the patient has been under close surveillance, has not required antitumor medication, and remains asymptomatic. PET/CT scans and bone marrow biopsy ruled out distant disease.

Biopsy Fixation Details

Our case Initially was evaluated on fine needle aspiration (FNA) and subsequent surgical excision of lymph node was performed (formaline fixation), which was analyzed by morphological, immunohistochemical (FOXP1 clon: JC12 GENNOVA), and molecular study (BCL2 and BCL6 rearrangements were performed with fluorescence in situ hybridization (FISH) (Agilent Technologies, TX, USA) and chain reaction of IGH polymerase (PCR)).

Frozen Tissue Available

Our case has frozen tissue available.

Details of Microscopic Findings

Our case showed cytomorphologic features a variety of small to intermediate-sized lymphocytes with subtle nuclear membrane irregularities, mitotic figures, and abundant tingible body macrophages in the background (Fig 1).

The histologycal morphology showed a follicular growth pattern with irregular, often compact, lymphoid follicles with attenuated mantle areas. The germinal centers lacked normal polarization while retaining a starry sky appearance and small reactive follicles, which displayed areas with a "node within a node" pattern. It consisted of a monotonous proliferation of blastoid cells with round/oval nuclei, fine chromatin, and small nucleoli (Fig 2). The bone marrow biopsy without evidence of lymphoma infiltration.

Immunophenotype

The neoplastic follicles were positive for CD20+, CD10+, BCL6+ and FOXP1 (Fig 3). BCL2 and MUM1, CD3, CD5, Cyclin D1, BCL2, MUM1, CD23, EMA, and EBER was negative (Fig 4).

Cytogenetics

No cytogenetic study has been performed.

Molecular Studies

The PCR detected IGH monoclonal rearrangement and FISH did not show signs of translocations for BCL2, BCL6 and MYC.

Proposed Diagnosis

Clinical, and morphologyc studies data lead to the conclusion that this is a case PTFL.

The 5th edition of the WHO classification of hematolymphoid tumors categorizes PTFL within follicular lymphomas with an age of onset under 40, with the average age between 2-25 years. Essential for its diagnosis is architectural distortion with a marked follicular growth pattern, high cellular proliferation with no rearrangement for BCL2, BCL6, MYC.

Interesting Feature(s)

Few cases of PTFL in middle age have been reported in the literature, such as the one we are describing. The diagnosis of PFTL is difficult and represents a challenge due to its cytologic and morphological characteristics similar to those of florid follicular hyperplasia and high-grade FL. However, correct interpretation of immunohistochemistry and demonstration of clonality in addition to limited-stage disease are essential to define the management of the patient.

EA4HP24-LYWS-441

How to classify recurrent indolent EBV positive T cell lymphoma with subcutaneous panniculitis-like T-cell lymphoma features in an adult patient?

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Case Description

A 20 year-old, female admitted to hospital with itchy, edematous, crusted lesions on arms on July 2006. The laboratory investigations and radiology were in normal. There was no evidence for vasculitis or autoimmune diseases. Bone marrow biopsy was normocellular. The skin 2006 was interpreted as EBV+ subcutaneous panniculitis-like T cell lymphoma. After one month of steroid therapy the nodules and excoriations all regressed and cleared. Electron beam therapy was also performed. Two recurrences 1 and 2 years after the diagnosis. The recurrent lesions were cleared with steroid therapy. There was no sign of systemic spread. She has been followed without further treatment till 2008. (The case was submitted 2011 SH-EAHP LA workshop Am J Clin Dermatol. 2010;11(2):147-50) She has been out of regular clinical follow-up from 2010 to 2023 without any complains and treatment. 15

years later in February 2023 she admitted to hospital with similar lesions on her bilateral legs with no evidence of systemic involvement by PET CT. Laboratory findings: Blood EBV PCR: 25099 copy/mL. Fallowing steroid therapy for 3 months, the lesions were regressed and cleared. She is under clinical follow-up without any lesion.

Biopsy Fixation Details

%10 buffered formalin

Frozen Tissue Available

no

Details of Microscopic Findings

The skin biopsy 2006 dense cellular infiltration in subcutaneous fat tissue, spreading to dermis. Both septal and lobular diffuse infiltration of fat tissue with scattered eosinophils and plasma cells. The characteristic rimming of fat cells present. There were also vascular invasion and ischemic necrosis of dermis. The biopsy of skin and subcutaneous tissue includes lesion appeared in 2023 is mainly composed of perivascular, small or medium size atypical lymphocyte infiltration, with associated few eosinophils. Although angiotrophism was noted, angioinvasion or angiodestruction was not prominent. Subcutaneous involvement was subtle.

Immunophenotype

The skin biopsy 2006 & 2008; The atypical lymphoid cells were diffuse CD3, CD8 and partially CD4, granzym, CD5 and CD7 positive. CD20, CD56 negative. EBER diffuse positive The skin biopsy 2023; infiltrative cells CD3 positive T cells, few grouping CD20 positive B cells. Most of the T cells were CD4 positive, the atypical lymphocytes were CD8 Tia1, perforin and granzyme, CD5 positive, Mild loss of CD7 expression, CD56 was negative. EBER diffuse positive . EBV (LMP-1), EBNA-2 study is pending.

Cytogenetics

No

Molecular Studies

2006 Clonal TCRd and TCRb rearrangement were detected. 2023 Clonal TCRd and TCRb rearrangement were detected.

NGS, no pathogenic and clinicaly relavant mutation present in genes involved in PIK3 kinasa or MTOR/AKT pathway

Proposed Diagnosis

Recurrent indolent EBV positive T cell lymphoma with subcutaneous panniculitis-like T-cell lymphoma features

Interesting Feature(s)

This is a case of cutaneous EBV related lymphoproliferative neoplasm involves dermal perivascular areas and subcutaneous fat. Regarded with the EBV positive cutaneous lesions it does not fit the criteria of Hydroa vacciniforme like lymphoma, Subcutaneous panniculitis-like T cell lymphoma, Systemic chronic active EBV disease, Severe mosquito bite allergy, EBV+NK-T cell lymphoma with its clinical presentation age of the patient and immunophenotypic characteristics. It’s a unique case with the pathologic and clinical features.

EA4HP24-LYWS-449

Indolent leukemic peripheral T-cell lymphoma with involvement of skin, bone marrow and lymph node

Prof. George Rassidakis, Dr. Ioanna Xagoraris, Dr. Elin Ljung, Dr. Anna Kwiecinska

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Case Description

- Female, 76 years old, with previous history of hypertension, stroke, depression, cardiac arrhythmias and multiple lung embolies. No known history of hematologic malignancies.
- 2019: First described skin lesions diagnosed as psoriasis on the hands treated with methotrexate and local ointments (no effect)
- 2022: Extensive erythroderma-like skin lesions treated with UVB (little effect)
- 2023 (April): Worsening of erythroderma-like lesions. A punch biopsy showed secondary involvement of the skin by mature T-cell non-Hodgkin lymphoma (NHL) without morphologic evidence of mycosis fungoides in the biopsy specimen
- 2023 (August-September): Bone marrow, peripheral blood and lymph node pathology showing stage IV (IPI 4), leukemic, mature T-cell NHL
- 2023 (October and December): Two additional punch biopsies showing involvement of the skin by mature T-cell non-Hodgkin lymphoma (NHL) without morphologic evidence of mycosis fungoides in any of these biopsy specimens
- The patient has received 3 out of 6 cycles CHOP-14 to date with radiological good response so far, however, the final evaluation of the treatment is pending. The patient is further admitted to the skin clinic for local treatment with steroids.

Biopsy Fixation Details

- The surgical specimen (lymph node) was fixed in neutral buffered formaldehyde 4% for 24 hours.

Frozen Tissue Available

Yes

Details of Microscopic Findings

The surgically excised lymph node showed partially preserved B-cell areas with well-formed, primary and secondary lymphoid follicles, the latter showing reactive germinal centres. The interfollicular T-cell areas are expanded and infiltrated by predominantly medium-sized lymphocytes with atypical nuclei. The neoplastic cells are intermingled with small reactive lymphocytes, histiocytes and a few plasma cells and eosinophils.

Immunophenotype

Immunohistochemistry showed that the neoplastic cells are positive for CD3, CD4, CD5, and PD1 and show partial loss of CD7. Decreased expression of CD2 and CD7. CD30 is positive in a small subset of neoplastic T-cells (<10%) cells. BCL6, CD8, CD10, CXCL13, Granzyme B, TBX21, ALK and TCL1 are negative in the neoplastic T-cell population. p53 is

also negative (wild-type p53 gene). The tumor cell proliferation as assessed by Ki67 is low (15-20%).
EBER1/2 ISH is negative.
Flow cytometric analysis showed a T-cell population (74%) with aberrant phenotype (CD3+, CD4+, CD8-, CD5+, CD7htr, CD26+, TCRb1+).

Cytogenetics

N/A

Molecular Studies

PCR analysis demonstrated the same clonal rearrangements of the TCR genes in multiple samples (peripheral blood, skin, lymph node).

Proposed Diagnosis

Indolent leukemic peripheral T-cell lymphoma with involvement of skin, bone marrow and lymph node.

Interesting Feature(s)

- Indolent course of a leukemic peripheral T-cell lymphoma with skin, bone marrow and lymph node involvement.
- No previous or co-existent mycosis fungoides. No T-prolymphocytic leukemia (TCL1-negative neoplastic T-cells)
- CD26+ neoplastic T-cell population by flow cytometry
- Discussion for sub-classification of leukemic, mature T-cell lymphomas with similar features (a new PTCL, NOS variant?)

EA4HP24-LYWS-454

Indolent T-cell lymphoma of the gastrointestinal tract

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Case Description

- 60 year old female
- Weight loss + ileocolonic Crohn's disease
- CT: long segment mid/distal small bowel thickening
- Balloon enteroscopy: small patches of "lymphangiectasia" → biopsied

Biopsy Fixation Details

5% buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

- Focal villous shortening with areas of epithelium showing vacuolated cytoplasm

- Multifocal superficial lamina propria sheets and nodules of small, monotonous, bland lymphoid cells
- No epitheliotropism or intra-epithelial component.

Immunophenotype

Immunohistochemistry

Positive: TCR beta, GATA3, BCL2, CD2, CD3, CD5, CD7, CD8

Positive: Granzyme B (about half of cells)

Weakly positive: CD20

Negative: CD4, CD10, CD25, CD30, CD56, perforin, PD1, ICOS, CXCL13, PAX5, CD79a, EBER ISH

Ki67 proliferation: <5%

Overlying epithelium: CK7 and adipophilin positive

Cytogenetics

None performed

Molecular Studies

TCR clonality studies: Monoclonal peaks of 269nt, 306nt, 215/224nt in tubes BA, BC2 and GA respectively

Proposed Diagnosis

Indolent T-cell lymphoma of the gastrointestinal tract with sebaceous metaplasia of the overlying epithelium

Interesting Feature(s)

- Weak CD20 expression (previously described by Wang et al., Diagn Pathol. 2018 Oct 20;13(1):82, PMID: 30342536)
- Granzyme B staining in subset of cells
- Overlying changes in the epithelium, interpreted as sebaceous metaplasia (unclear if related to T-cell lymphoma)
- T-LPD present in 2015 small bowel biopsies for Crohn's disease
- As of 2024, on adalimumab for Crohn's disease, but no symptoms from T-cell lymphoma (~8 years)

EA4HP24-LYWS-460

Monocytoid B-cell non-Hodgkin lymphoma with TFH cell proliferation

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Case Description

- 41-year-old man presented with abdominal pain for 2 months.
- PET-CT:
  - FDG avid irregular circumferential wall thickening involving the ascending colon, caecum, IC junction and terminal ileal loops.
  - Left cervical level IB, few left axillary level I, aortocaval and paraaortic, right internal and external iliac and bilateral inguinal
- Colonic biopsies revealed ulceration with inflammation and external iliac lymph node core biopsy was also non-diagnostic.
- Left axillary lymph node excisional biopsy was obtained.

Biopsy Fixation Details

10% phosphate buffered fomalin

Frozen Tissue Available

not available

Details of Microscopic Findings

- Areas of expanded and effaced interfollicular architecture by admixed population of sheets of cells of monocytoid/histiocytoid morphology, intermediate-sized lymphoid cells, small lymphoid cells, and very few eosinophils.
- The interspersed preserved follicles show relatively maintained architecture.

Immunophenotype

Within the interfollicular areas:

- Monocytoid/histocytoid cells in the interfollicular areas:
  - Positive for CD20, MUM1, Pax5 (weak), and TBX21
  - Negative for CD10, kappa and lambda light chains, and T-cell markers
- Predominant population of small to intermediate-sized lymphoid cells:
  - Positive for CD3, CD7, PD-1, ICOS, and CD4>CD8 (few of the small lymphoid cells are positive for GATA3)
  - Negative for CD1a, TBX21.
- Additionally, few small lymphoid cells are positive for CD20.

- CD123 marked admixed plasmacytoid dendritic cells.
- No CD10 positive cells seen in the interfollicular areas.
- Ki67/MIB1 labeled most of the monocytoid/histiocytoid cells while being insignificant in the T-lymphoid cells.The follicles:
- CD20 and Pax-5 mark the follicles; CD21 reveals the distortion of the follicular dendritic cell [FDC] meshwork in these native follicles and also labels the marginal zones; however no extrafollicular FDC proliferation was identified.
- CD10 is weakly positive in the germinal centresNeither of the cell population expressed EBERs.

Cytogenetics

Not done

Molecular Studies

- Clonality evaluation:
  - A dominant peak was observed (which is consistent in varying template concentrations) in a background small peaks
  - No dominant peaks were detected for IGH tube A, IGH-tube C, TCR gamma and TCR Beta.
- NGS based targeted panel evaluation:
  - TNFRSF14 exon 5 indel and PTEN exon 9 SNV

Proposed Diagnosis

- Monocytoid B-cell non-Hodgkin lymphoma with florid T-lymphoid cell proliferation of follicular T-cell immunophenotype

Interesting Feature(s)

- Histoarchitecture is more like FTH cell lymphoma
- Abnormal phenotype of interfollicular B-lymphoid cells
- Abnormal immunoarchitecture for T-lymphoid cells. •Ki-67 expression restricted to B-lymphoid cells
- Clonal B-lymphoid cells, however T-lymphoid cells are non-clonal (there is adequate representation of T-lymphoid cells).
- TNFRSF14 exon 5 indel and PTEN exon 9 SNV
  These findings along with immunohistomorphological features are of B-cell non-Hodgkin lymphoma of monocytoid morphology with dominant reactive FTH cells.

EA4HP24-LYWS-462

A case of Duodenal-type follicular lymphoma.

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Case Description

55 year old female presented in November 2018 with epigastric and right sided abdominal pain for 5-6 months. There was no associated weight loss or rectal bleeding. There was no evidence of lymphadenopathy or hepatosplenomegaly on examination.

A past medical history of Type 2 Diabetes Mellitus, Hypercholesterolemia and Acid peptic disease was elicited. Her drug history includes Lansoprazole, Metformin and Atorvastatin.

She underwent an oesophagogastroduodenoscopy and a white plaque-like appearance was seen in the mucosa in the second stage of the duodenum. A biopsy of the lesion showed an atypical lymphoid proliferation in keeping with follicular lymphoma. She was then referred to the Haemato-oncology team. A PET scan confirmed localised disease as no evidence of metabolically active disease was present elsewhere. She was diagnosed with duodenal follicular lymphoma duodenum stage 1 grade 1.

She is currently on Expectant management (watch and wait) and attends clinic every 6 months. She remains stable with no symptoms and no progression of the disease.

Biopsy Fixation Details

10% neutral buffered formalin.

Frozen Tissue Available

None

Details of Microscopic Findings

Small bowel mucosal biopsies with prominent lymphoid infiltrate that is organised into lymphoid follicles with follicular centres showing lack of zonation and absence of tingible body macrophages - features that are suspicious of follicular lymphoma. The follicles show a mixture of centrocytes and centroblasts with the former predominating. The centroblasts are less than 5 per high power field. There is no evidence of transformation.

Immunophenotype

Immunohistochemistry shows that the follicles express CD20, bcl-6, CD10 and bcl-2. There is no expression of CD5, CD23 or CD21. The latter two stains show a preserved and inverted follicular dendritic cell meshwork pattern. The proliferation fraction is <5%.

Cytogenetics

None performed

Molecular Studies

None performed

Proposed Diagnosis

Primary 'duodenal type' follicular lymphoma

Interesting Feature(s)

A classic case of the new entity. No therapy has been initiated and patient is stable. This aligns with the reported excellent prognosis associated with this entity.

EA4HP24-LYWS-463

Primary cutaneous marginal zone lymphoma

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Case Description

·A 49-year-old lady presented with swelling over nape of neck for 1 month.

·No B symptoms were present.

·An excision biopsy of the swelling was performed and represenative one paraffin block was refered.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

·Dense dermal infiltrate of small lymphoid cells with vague confluent nodular-like organization and infiltration into the subcutaneous fat.

·The overlying epidermis was intact. No epidermotropism was identified.

·Occasional scattered larger cells and plasma cells were seen at the periphery of the infiltrate.

Immunophenotype

·The cells are positive for CD20 and Pax-5 positive cells. CD21 reveals presence of FDC meshwork within the nodular aggregates of CD20/Pax-5 positive B-lymphoid cells. The B-lymphoid cells within the FDC meshwork were also positive for LMO2; while negative for CD43.

·CD123 revealed few clusters of plasmacytoid dendritic cells around the nodules of CD20/Pax-5 positive cells, CD138 marked the collar of plasma cells, and CD30 marked the larger cells.

·CD3 highlighted the admixture of T-lymphoid cells which showed retained expression for CD7 and CD4>CD8.

·Ki67/MIB1 labeling index was ~15-20%.

Cytogenetics

Not done

Molecular Studies

Not done

Proposed Diagnosis

•Low grade B-cell non-Hodgkin lymphoma- primary cutaneous marginal zone lymphoma with plasma cell differentiation

Interesting Feature(s)

•Primary cutaneous marginal zone lymphoma (cMZL) is a rare indolent lymphoma accounting for 2-7% of all cutaneous lymphomas and ~10% of all marginal zone lymphomas.

•Demonstration of PDCs around the B-lymphoid cell nodules, are suggestive of cMZL over primary cutaneous follicular lymphoma.

EA4HP24-LYWS-465

Dominant clonal T-cell proliferation with associated clonal B-cell proliferation: is it a composite T & B cell lymphoma?

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Case Description

- 47-year-old man presented with gradual left sided abdominal distension for 1 month associated with dragging sensation.
- B symptoms were present (significant weight loss)
- On examination, bilateral inguinal lymph nodes were palpable; largest measuring 3cm.

Biopsy Fixation Details

10% buffered formalin

Frozen Tissue Available

Not available

Details of Microscopic Findings

- Histomorphology showed effaced nodal architecture by small to intermediate-sized atypical lymphoid cells arranged in sheets with patchy areas of vague nodularity.
- These atypical cells were relatively monomorphic with scant eosinophilic cytoplasm, fine granular chromatin, and small nucleoli.

Immunophenotype

Immunohistochemistry on the tissue biopsy:

- The sheets of atypical cells showed positivity for CD3, CD43, CD5, TIA-1, CD2 (variable), and CD20 (weak).
  - These cells were negative for Tdt, CD4, CD8, Bcl-6, PD1, TBX21, CD123, CD103, CD57, Pax-5, MUM1, CD200, and CD79a.
  - CD10 and GATA3 were equivocal
  - Few scattered CD7, CD4 and CD8 positive cells were seen
- Intervening nodular aggregates of CD20 strongly positive cells were seen, which were positive for CD19, CD79a, Pax-5, cyclin D1 and IgD; weakly positive for CD21; while negative for SOX-11, CD200, IgG, CD43 & CD23.
  - CD5 was equivocal in these cells.
- CD21 and CD23 did not reveal any follicular dendritic cell meshwork.
- MIB-1 labeling index was approximately less than 5%.
- EBER is negative.Flow cytometric immunophenotypic findings:
- Immunophenotypic findings revealed 58.93% abnormal T lymphoid cells and 22.95% clonal B lymphoid cells.
- The T lymphoid cells expressed CD49d, CD2, and CD5; while were negative for CD4, CD8, CD7, and CD30.
- The abnormal clonal B cells expressed only dim to negative CD5 and showed surface kappa light chain restriction.

Cytogenetics

Not done

Molecular Studies

- Clonality evaluation is uninterpretable due to lack of inadequately amplifiication
- NGS based targeted evaluation revealed the following:
  - CCND1 exon 1 missense mutation
  - TET2 exon 8 indel and
  - Gains of CXCR4, HIST1H1E, & BTG1

Proposed Diagnosis

- Mature T-cell non-Hodgkin lymphoma with associated clonal B-lymphoid cell proliferatio (in view of clinical finding of splenomegaly, a differential diagnosis of hepatosplenic T-cell lymphoma with CD5 positivity was considered) with associated clonal B-lymphoid cell proliferation with shared phenotype of cyclinD1 positive mantle cell lymphoma.

Interesting Feature(s)

- Co-existence of T cell non-Hodgkin lymphoma with abnormal B-lymphoid cells; the immunophenotype of abnormal T cells was unusual and not typical of any of the well-defined entities viz. T-PLL, follicular helper T cell lymphoma, Adult T cell leukemia/lymphoma or Anaplastic large cell lymphoma.
  - Though a close differential of hepatosplenic T cell lymphoma was considered in the light of clinical history, these are known to be CD5 negative and express CD7.

- Associated clonal B-cell proliferation with mantle cell lymphoma-likeimmunophenotype of the B-cells in this case is an unusual finding.
- Presence of CCND1 exon 1 missense mutation, TET2 exon 8 indel and gains of CXCR4, HIST1H1E, BTG1 – these findings corroborate with the finding of cyclin D1 positive B-lymphoid cells and the dominant clonal T-lymphoid cell proliferation.The overall features are of composite mature T and B-cell lymphoma

EA4HP24-LYWS-471

Indolent primary cutaneous lymphoproliferative disorder with overlapping features between primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (LPD) and primary cutaneous marginal zone LPD.

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Case Description

A 43 year-old man with presents with slow growing skin nodule on the forearm that was excised. Systemic/extracutaneous symptoms were absent. Hemogram was normal. Staging CT-scan did not reveal adenopathies; peripheral blood and bone marrow work-up showed no abnormalities. After one year of follow-up under watch-and-wait the patient is assymptomatic without local recurrence or new skin lesions

Biopsy Fixation Details

10% neutral buffered formalin

Frozen Tissue Available

No

Details of Microscopic Findings

Vaguely nodular/diffuse dense lymphoid proliferation centered in the dermis, composed of small and intermediate-sized atypical lymphocytes, in a background of histioctyes and plasma cells, with predominant periadnexal distribution; rare nucleolated atypical large cells were present. Occasional lymphoid aggregates devoid of preserved germinal centers and high endothelial venule proliferation were observed as well as focal epidermotropism without indian filing/Pautrier microabcesses. Plasma cells were more abundant at the periphery of the lesion

Immunophenotype

Lymphoid aggregates were mostly composed of small B cells(CD20+/CD3-/CD10-/BCL6-/CD5-/CylinD1-); small/intermediated-sized cells were predominantly CD4+T-cells with preseved pan-T-cells markers (CD3+/CD2+/CD5+/CD7+), expressing PD1 (namely in epidermotropic lymphocytes and at clusters/rosettes surrouding large cells) and, focally,

ICOS. Large cells: CD30+/-; plasma cells: λ light-chain restriction (IgG). EBER-ISH was totally negative

Cytogenetics

Not performed

Molecular Studies

PCR analysis (BIOMED-2) disclosed both T-cell clonality (clonal rearrangements of TCRγ and TCRβ genes) and B-cell clonality (two clonal rearrangements of kappa genes; heavy chain gene analysis disclosed an irregular polyclonal pattern suggestive of somatic hypermutation). Retrospectively, a previous diagnosis of perivascular dermatitis in the proximal lower limb is being reavaluated for the presence of the same B-cell and T-cell clones

Proposed Diagnosis

Indolent primary cutaneous lymphoproliferative disorder with overlapping features between primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (LPD) and primary cutaneous marginal zone LPD

Interesting Feature(s)

1 – The case illustrates that the diagnostic boundaries between primary cutaneous marginal zone LPD and CD4+ small/medium T-cell LPD are presently unclear.

2 - The clonallity results illustrate that these lesions may arise in the setting of chronic inflammatory stimuli over (at least) B-cells.

3 – Since the case illustrates a class-switched type of cutaneous MZ LPD, described as richer in PD1+ T-cells, is it biologically meaningful and/or diagnostically usefull to divide cutaneous MZ LPD into class-switched and non-class-switched cases?

Panel Diagnosis Session V

Panel Diagnosis: Primary cutaneous marginal zone lymphomas/LPD and extranodal MZL involving subcutaneous tissue or conjunctiva

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-22	PC-MZLPD, class-switched	.....
EA4HP24-LYWS-47	EBV+PC-MZLPD, class-switched	Transformation to large and plasmablastic lymphoma
EA4HP24-LYWS-115	PC-MZL non-class-switched	Parotid gland and LN involvement *MYD88* WT done by the panel
EA4HP24-LYWS-296	PC-MZL	
EA4HP24-LYWS-360	PC-MZL epidermotropic	CXCR3+ done by the panel
EA4HP24-LYWS-463	PC-MZL	Clonality was not done
EA4HP24-LYWS-241	Extranodal MZL, class-switched	IGG4+, conjunctival lesion History of PC-MZLPD
EA4HP24-LYWS-6	Extranodal-MZL, class-switched	Involving subcutaneous tissue
EA4HP24-LYWS-351	Extranodal MZL	Involving subcutaneous tissue *MYD88* WT

Panel Diagnosis: Cases with overlapping features between PC-MZL(LPD and PC CD4+ T-cell LPD

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-303	PC-MZLPD class-switched overlapping with CD4+T-cell LPD	IGH clonal TR clonal
EA4HP24-LYWS-192	PC-MZLPD class-switched rich in TFH cells	IGH clonal TR polyclonal
EA4HP24-LYWS-290	PC-MZLPD overlapping with CD4+ T-cell LPD	IGH clonal TR clonal
EA4HP24-LYWS-471	PC-MZLPD class-switched overlapping with CD4+ T-cell LPD	IGH clonal TR clonal

Panel Diagnosis: Primary cutaneous CD8+ T-cell LPD

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-167	PC-CD8+ T-cell LPD	
EA4HP24-LYWS-229	PC-CD8+ T-cell LPD	

Panel Diagnosis: Primary cutaneous marginal zone lymphomas/LPD and extranodal MZL involving subcutaneous tissue or conjunctiva

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-246	iT-LBP	Parotid gland with carcinoma
EA4HP24-LYWS-60	iT-LBP	With FL
EA4HP24-LYWS-74	iT-LPB	Parotid gland with acinar cell carcinoma
EA4HP24-LYWS-117	iT-LPB	In Tonsils
EA4HP24-LYWS-183	iT-LPB	Ovarian metastasis
EA4HP24-LYWS-266	iT-LPB	Castleman disease
EA4HP24-LYWS-315	iT-LPB	Castleman disease and FDC sarcoma
EA4HP24-LYWS-373	iB-LPB	Reactive LN

Panel Diagnosis: Cases raising the differential diagnosis with indolent T-lymphoblastic proliferation

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-35	Residual Thymus with NEC	
EA4HP24-LYWS-215	True thymic hyperplasia	
EA4HP24-LYWS-290	T-LBL	Protracted clinical course

Panel Diagnosis: Transient clonal CD8+ T-cell LPD response

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-344	Reactive, clonal CD8+ T-cell LPD	Squamous cell carcinoma
EA4HP24-LYWS-276	Reactive, clonal CD8+ T-cell LPD	Celiac disease and viral infection
EA4HP24-LYWS-330	Reactive, clonal CD8+ T-cell LPD	Infectious mononucleosis

Panel Diagnosis: Lymphocyte variant of hypereosinophilic syndrome

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-212	LV-HES	PB and BM involvement
EA4HP24-LYWS-380	LV-HES	Skin involvement, BM and PB

Panel Diagnosis: PD1+ T-cell proliferations

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-361	TFH lymphoma, indolent	TR clonal, *TET2* and *RHOA* mutations, 73 months, no Tx.
EA4HP24-LYWS-408	PD1+ clonal skin proliferation	Favors Sezary syndrome
EA4HP24-LYWS-449	PD1+ clonal leukemic, skin, LN LPD	Favors Sezary syndrome

Panel Diagnosis: EBV-positive, B, T or NK-cell lymphoproliferations

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-340	Extranodal NK-T-cell lymphoma	Recurrent lesion
EA4HP24-LYWS-293	Extranodal NK/T-cell type	Indolent, CD56-
EA4HP24-LYWS-250	CAEBV progressed to T-cell lymphoma	
EA4HP24-LYWS-61	Polymorphic, EBV+ B-cell LPD	HIV+ patient, recovered with ART
EA4HP24-LYWS-363	DLBCL associated with chronic inflammation	
EA4HP24-LYWS-138	Polymorphic, EBV+ B-cell LPD	HIV+ patient under ART

Panel Diagnosis: Composite lymphoma

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-465	Composite lymphoma PTCL+MCL	

Panel Diagnosis: Indolent T/NK-cell lymphoproliferative disorder of the gastrointestinal

Case	Panel Diagnosis	Features/comments
EA4HP24-LYWS-24	IT LPD-GI	CD4- CD8-, PD1+ Ki67 5% TR monoclonal, NGS *FAT1*
EA4HP24-LYWS-328	IT LPD-GI	CD4- CD8- CD20+ Ki67 <5% TR monoclonal, No mutations.
EA4HP24-LYWS-349	IT LPD-GI	CD8+ CD4- PD1- Ki67 <5% TR monoclonal, NGS *STAT5B*, *IRF8* VUS
EA4HP24-LYWS-454	IT LPD-GI	CD8+ CD4- CD20+ PD1- Ki67 <5% TR monoclonal
EA4HP24-LYWS-211	DLBCL EBV- in pt with past history of IT LPD-GI treated with MTX and CTX	CD8+ CD4- CD20- PD1- Ki67 <5% TR monoclonal
EA4HP24-LYWS-79	Indolent NK-cell lymphoproliferation of the gastrointestinal tract.	NK+ CD20- TR polyclonal *JAK3* mutation

Panel Diagnosis: Indolent clonal T cell LPDs of the GI with unusual features

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-461	IT LPD-GI	GI wall layers extension CD8+ CD20- PD1- KI67<5% TR monoclonal, NGS *DNMT3A* mutation (clonal hematopoiesis)
EA4HP24-LYWS-253	IT LPD-GI	GI wall layers extension CD4+ CD20- PD1- KI67<5% TR monoclonal Diagnosed as PTCL NOS treated with BMT and relapsed 10 y later
EA4HP24-LYWS-256	IT LPD-GI	GI wall layers extension with clusters of NK-cells mesenteric LN CD8+ CD20- PD1- KI67<5% TR monoclonal

EA4HP24-LYWS-96	IT LPD-GI	GI wall layers extension mesenteric LN + Splenomegaly CD4+ CD7- CD20+ PD1- KI67<5%

Panel Diagnosis: Other T-cell LPDs involving the gastrointestinal tract

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-337	Favors the diagnosis of indolent, systemic, CD4+ T-cell lymphoma/LPD (with LN, BM and intestinal involvement).	with nodal initial presentation +. wall layers extension, BM and indolent behaviour TR monoclonal, *STAT3* mutation CD4+, **PD1+,** Ki67-low
EA4HP24-LYWS-364	Favors the diagnosis of indolent, systemic, CD4+ T-cell lymphoma/LPD (with LN, intestine, PB and BM involvement) progressing to a systemic aggressive T-cell lymphoma, NOS	With nodal and wall layers extension, PB and BM Progression to clonally related aggressive lymphoma Aberrant CD20+, CD57+, ICOS+ TR monoclonal (identical in all lesions) NGS (LN +). *JAK1* and *TET2* CD4+, **PD1+,** Ki67>20%
EA4HP24-LYWS-376	Favors the diagnosis of indolent, systemic, CD4+ T-cell lymphoma/LPD (with LN, skin and epiglottis involvement).	epiglottis presentation with past history of LN and skin T cell lymphoproliferation Same T cell clone (all lesions) NGS no mutations CD4+, **PD1+-,** Ki67>10%
EA4HP24-LYWS-191	Oligoclonal T cell expansion in an inflammatory bowel disease	Deep lymphoid aggregates CD4>CD8; Ki67<5% Oligoclonal T cell proliferation

Panel Diagnosis: Intestinal indolent BCL: DFL (5 cases), and duodenal MALT lymphoma (1 case)

Case	Panel Diagnosis	Features/comments
EA4HP24-LYWS-165	Duodenal FL	Duodenal and ileum involvement WW 5y FU with persistent DFL
EA4HP24-LYWS-322	Duodenal FL	*BCL2*-R *CREBBP* (4308T>G, VAF =28%) *HVCN1* (425T>G, VAF=27%) *KMT2D* (5113A>T, VAF =27%)
EA4HP24-LYWS-378	Duodenal FL	NA
EA4HP24-LYWS-404	Duodenal FL	NA
EA4HP24-LYWS-462	Duodenal FL	NA
EA4HP24-LYWS-396	Low grade B-cell lymphoma more consistent with MALT	B CD10- BCL2+ CD138 weak No FDC FISH *BCL2*-R negative *CD79b* mutation

Panel Diagnosis: Other indolent FL/FL-like lesions

Case	Panel Diagnosis	Features/comments
EA4HP24-LYWS-317	Follicle center lymphoma of the lower female genital tract.	*BCL6*-R+, *BCL2*-R- (gain), *MYC*-R- *TNFRSF14* S1pR2 IGLL5, EZH2
EA4HP24-LYWS-338	Extranodal FL with *BCL2*-R and *MYC*-R	*BCL2*-R+ *MYC*-R+ I*RF4*-R- W&W no recurence 2y FU
EA4HP24-LYWS-100	skin involvement by a FL grade 1-2	*BCL2*-R+ focal B cell clone

Panel Diagnosis: Atypical follicle with genetic alteration

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-38	incipient Burkitt lymphoma	One atypical follicle with *MYC*-R+ *BCL2*-R/*BCL6*-R negative
EA4HP24-LYWS-31	Atypical follicle with *BCL6* polysomy	One atypical follicle, *BCL6*-R negative but *BCL6* gain

Panel Diagnosis: Miscellaneous B-cell proliferations_ Others indolent B cell LP/lymphoma

Case	Panel Diagnosis	Unusual Features
EA4HP24-LYWS-358	indolent MCL	no lymphocytosis/no LN *CCND1::IGH* (23%) + *BIRC3/MALT* negative
EA4HP24-LYWS-407	Leukemic non-nodal MCL with plasmocytic differentiation	intraocular lesion & with plasmocytic differentiation, *CCND1*-R+, B cell clone *MYD88*^{S219C} but no *MYD88*^{L265P} mut
EA4HP24-LYWS-386	CD123- BRAF- Hairy cell leukemia	*MAP2K1* & *CREBBP* mutations No *BRAF*
EA4HP24-LYWS-419	Cold agglutinin disease/ Primary cold agglutinin disease	marked erythrophagocytosis.
EA4HP24-LYWS-460	TFH rich MZL	B cell clone, No T cell clone NGS *TNFRS14, PTEN* (germline?)
EA4HP24-LYWS-420	consistent with MALT lymphoma	Lung nodules B cell clone; t(11,18)- *MYD88*^{L265P} 3%