NYU Langone Health

DEPARTMENT OF PATHOLOGY

Case of the Week

Hematopathology: Atypical lymphoid hyperplasia associated with B-cell immunodeficiency

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History

The patient is a 29 year-old male with a past medical history of hypothyroidism who presents with fever of unknown origin. One year previously, he presented to his primary care physician with fever and mouth sores and was told he had “abnormal liver tests” (alkaline phosphatase 600s, low iron), which resolved on follow-up after 2 months. Five to six months previously, he had recurrence of fever and mouth pain and was found to be “pancytopenic,” with improvement on one-month follow-up. Referrals to Hematology, GI, and Immunology resulted in negative workups for HIV, EBV, and hepatitis. Five weeks prior to presentation he developed fever that failed to resolve with multiple courses of antibiotics. He was admitted to the hospital for further workup, which was significant for neutropenia (WBC 1.9), hyponatremia (127), and elevated alkaline phosphatase (1202). Imaging showed bilateral pleural effusions, hepatomegaly, splenomegaly with multiple hypodense lesions, and bilateral external iliac and inguinal lymphadenopathy. Lymph node and bone marrow biopsies were performed. Lymph node, bone marrow, and pleural fluid were also sent for flow cytometry and showed almost complete absence of mature B-lymphocytes.

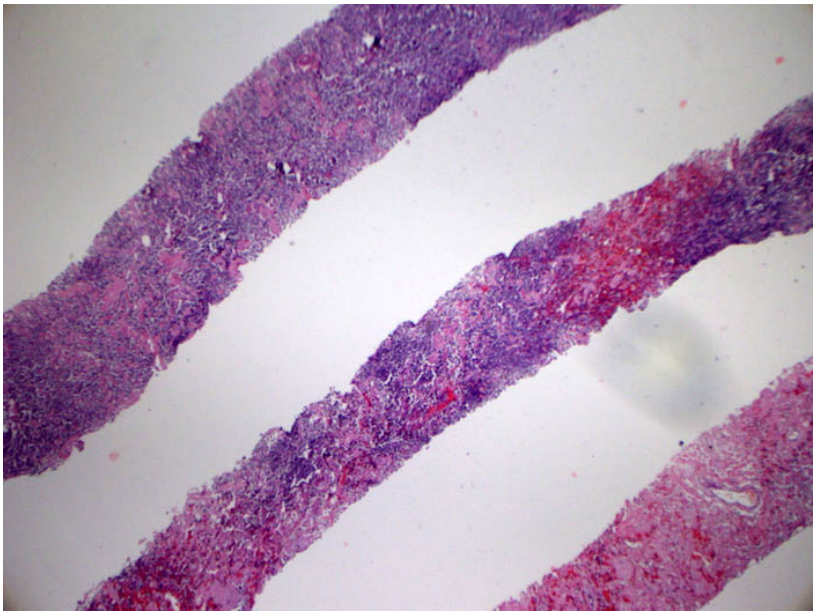

Figure 1: Lymph node core biopsy, 40x magnification

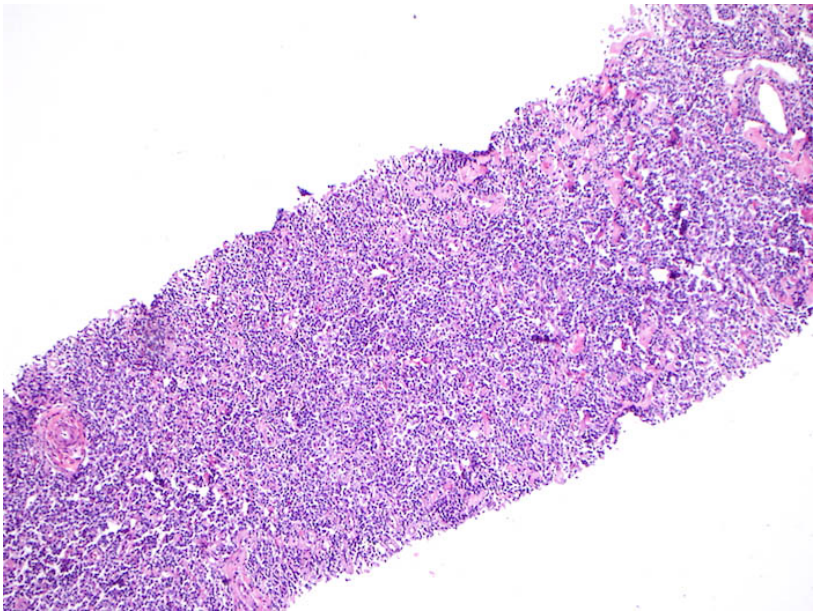

Figure 2: Lymph node core biopsy, 100x magnification

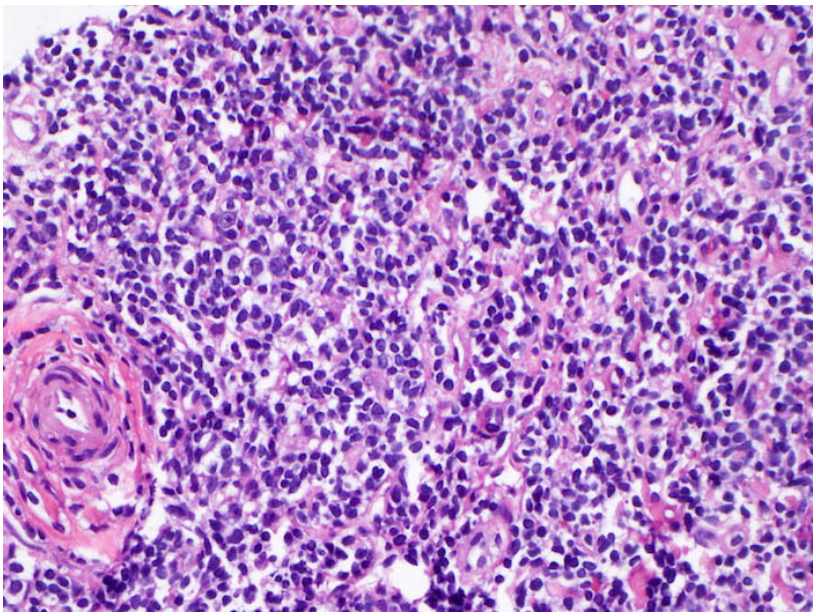

Figure 3: Lymph node core biopsy, 400x magnification

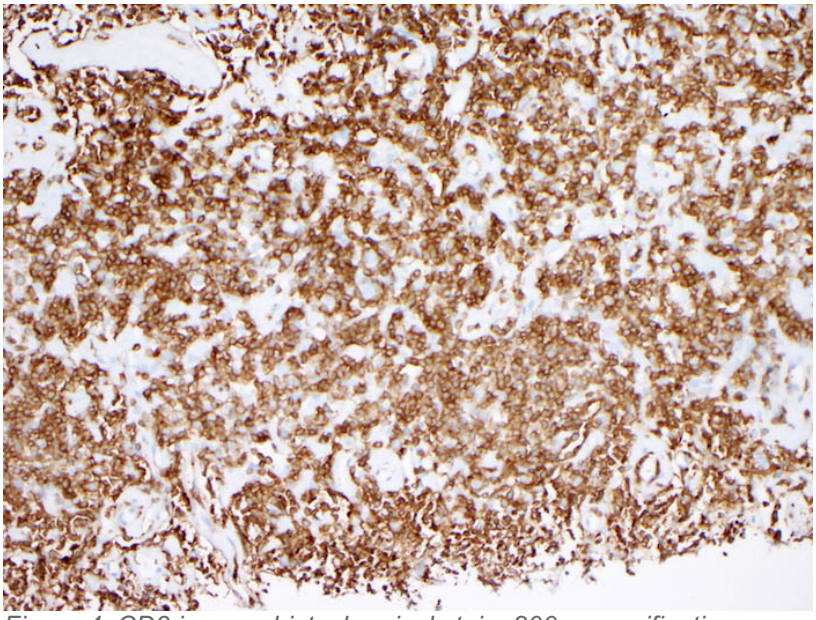

Figure 4: CD3 immunohistochemical stain, 200x magnification

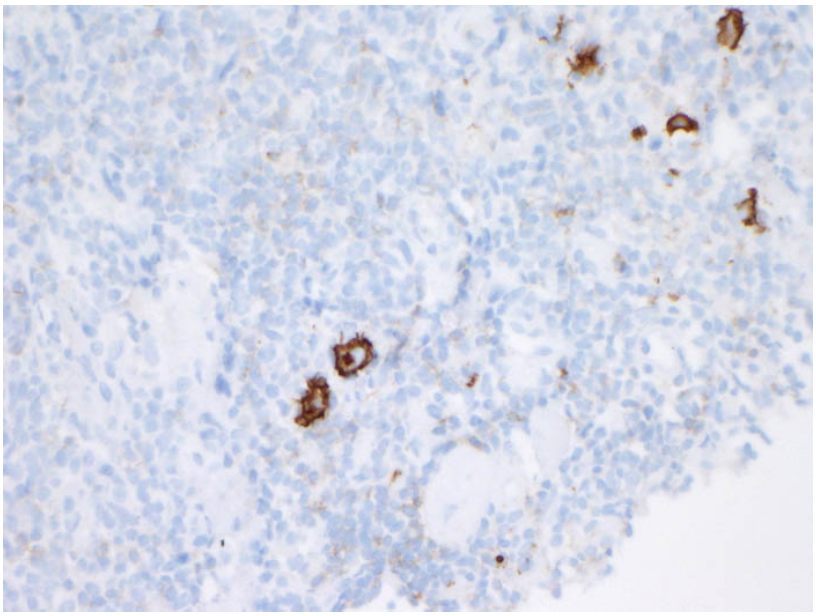

Figure 5: CD20 immuohistochemical stain, 400x magnification

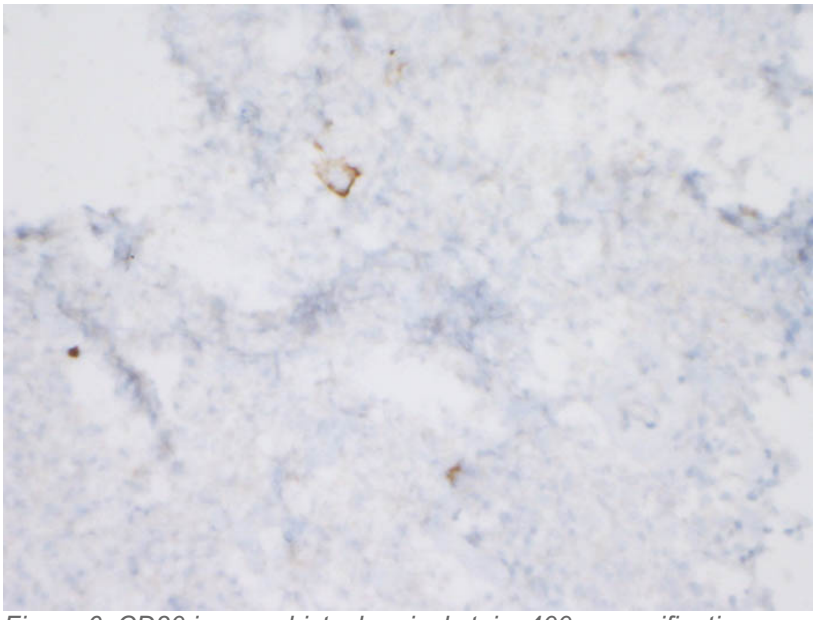

Figure 6: CD30 immunohistochemical stain, 400x magnification

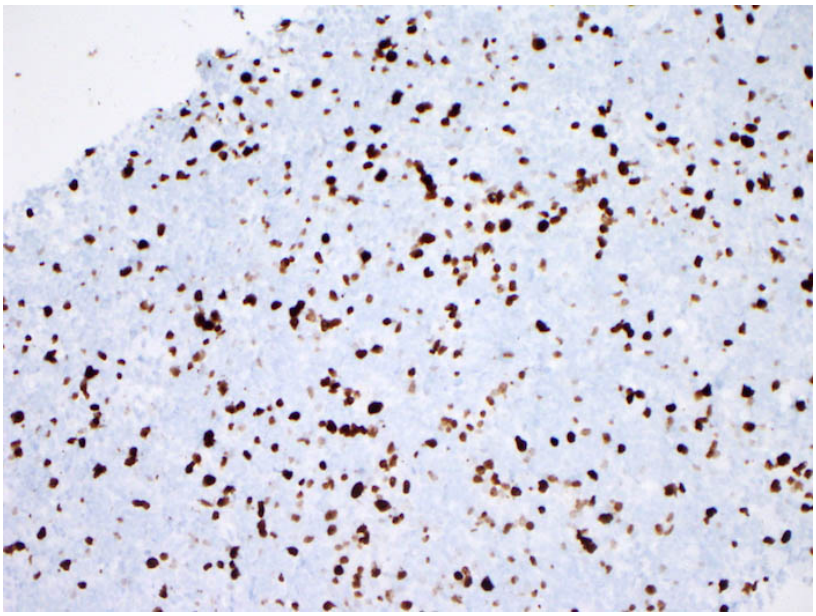

Figure 7: Ki-67 immunohistochemical stain, 400x magnification

Figures 1-7

Figures 1-3. Fig. 1: Core biopsy of an inguinal lymph node shows poorly defined nodular architecture (H&E, 40x magnification). Fig. 2: The lymphoid tissue consists of polymorphic small lymphocytes surrounding sinusoids (H&E, 100x magnification). Fig. 3: Few large, atypical cells are identified within the lymphocyte aggregates (H&E, 400x magnification).

Figures 4-6. Fig. 4: Immunohistochemical stain for CD3 highlights the small lymphocytes (membranous, 200x magnification). Fig. 5: The large cells are positive for CD20 (membranous, 400x magnification). Fig. 6: CD30 shows weak reactivity (membranous, 400x magnification). Fig. 7: Ki-67 highlights the large cells and occasional small lymphocytes (nuclear, 400x magnification).

Other immunohistochemical stains performed: Pax-5 and CD79a are positive only in the large cells. CD15 and EBER are negative. The bone marrow biopsy also shows aggregates of CD3-positive small lymphocytes with few large central cells positive for CD20 and CD79a.

Diagnosis

Atypical lymphoid hyperplasia associated with B-cell immunodeficiency

Discussion

Introduction
The patient is a young male presenting with fevers of unknown origin over a 1-year duration, lymphadenopathy, hepatomegaly, splenomegaly with multiple lesions, and pleural effusions. Lymph node and bone marrow biopsies show aggregates of predominantly small T-lymphocytes with central large, atypical, proliferative cells showing immunoreactivity to B-cell markers. Flow cytometry on all three specimens is notable for absence of mature B-lymphocytes, concerning for a B-cell immunodeficiency. The differential diagnosis includes Hodgkin lymphoma (classic versus nodular lymphocyte-predominant type), T-cell/histiocyte-rich large B-cell lymphoma, and immunodeficiency-associated atypical lymphoid hyperplasia.

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) was initially classified as a subset of diffuse large B-cell lymphoma; however in the 2008 WHO it was re-classified as a separate entity.[1] THRLBCL is characterized by <10% of large neoplastic B-cells within a background of mostly reactive T-lymphocytes and histiocytes.[1,2] Patients present at a younger median age (4th decade of life) than with DLBCL, and there is a male predominance.[1,2] As with Hodgkin lymphoma, systemic "B-symptoms" are often present, although THRLBCL is typically higher stage at presentation, with involvement of organs such as liver and spleen.[1,2]

Atypical lymphoid hyperplasia has been reported in association with common variable immunodeficiency (CVID), a heterogeneous group of disorders associated with arrest of normal B-lymphocyte differentiation and resultant hypogammaglobulinemia.[3] Patients with CVID have an increased incidence of both non-Hodgkin lymphoma and localized or generalized lymphadenopathy.[3] At biopsy, these lymphoid proliferations can be markedly atypical and difficult to distinguish from lymphoma.[3]

Microscopic findings
All three entities can show partial to complete effacement of normal lymph node follicular architecture.[1,2,3] In both Hodgkin lymphoma and T-cell/histiocyte-rich large B-cell lymphoma, few large, neoplastic cells are seen within a stroma of benign reactive lymphocytes and/or histiocytes.[1,2] In atypical lymphoid hyperplasia associated with immunodeficiency there is expansion of the paracortical zone within the lymph node, primarily by histiocytes and small (usually CD4-positive) reactive T-lymphocytes.[3] Germinal centers and/or sinuses contain large, atypical cells that may resemble Reed-Sternberg cells.[3]

Immunohistochemistry
The neoplastic cells of classic Hodgkin lymphoma are usually negative for B-cell markers CD20 and CD79a and positive for CD30 and CD15.[1,2] The reverse is true in T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), which is positive for all B-cell markers, rarely positive for CD30, and negative for CD15.[1,2] However, nodular lymphocyte-predominant Hodgkin

lymphoma (NLPHL) cells show the same phenotype as THRLBCL.[1,2] The distinguishing feature in these two entities is the background cell population, which is predominantly CD3+ T-lymphocytes and CD68+ histiocytes in THRLBCL and a mixed population including CD20+ B-cells and CD21+ follicular dendritic cells in NLPHL.[1,2] THRBCL also shares immunophenotypical characteristics with non-GC diffuse large B-cell lymphoma, including non-reactivity for CD10 and variable reactivity for Bcl-2.[1,2] The large cells in atypical lymphoid hyperplasia are also positive for B-cell markers, and the background reactive cell population consists of histiocytes and T-cells with an increased CD4 to CD8 ratio.[3]

Genetics

B-cell immunoglobulin chain rearrangements should be present in THRLBCL; however, their detection is difficult due to the low neoplastic to reactive cell ratio.[1] Abnormalities in chromosomes 4q and 19p have been reported in both THRLBCL and NLPHL, suggesting a possible common precursor.[1] However, gene expression profiles differ between the two entities: the histiocyte-rich expression of THRLBCL is associated with down-regulation of T-cell mediated immune surveillance, which is thought to be the mechanism for the tumors to escape "rejection" by the host immune system and have a more aggressive clinical course.[1] Atypical lymphocyte hyperplasia is by definition a reactive process, with polyclonal B- and T-lymphocytes.[3]

Management

THRLBCL has a similar clinical course and prognosis to diffuse large B-cell lymphoma, necessitating more aggressive treatment.[1,2] NLPHL, despite similar tumor morphology and immunohistochemical phenotype, typically presents at an earlier stage and follows a more indolent clinical course.[1,2] Atypical lymphocyte hyperplasia associated with immunodeficiency is a mimicker of lymphoma but does not necessarily progress to lymphoma.[3,4] In a series of 30 cases of nodal and extranodal lymphoid proliferations in 17 patients with CVID, two were given a diagnosis of intermediate to high grade lymphoma, three were called lymphoma at initial diagnosis but revised to atypical lymphoid hyperplasia on review, and the remainder were reactive/infectious.[3] At follow-up, 6 of 16 patients died of infectious complications, and none died of lymphoma.[3] Of patients with immunodeficiency, particularly CVID, the most common lymphoma is MALT/marginal zone, due to the increased malignant transformation risk with sustained immune activation and proliferation.[4] Thus, although atypical lymphoid hyperplasia associated with B-cell immunodeficiency is a benign diagnosis, it does warrant close follow-up and management of infections and associated inflammation.

References

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2. Abramson JS (2006). T-Cell/Histiocyte-Rich B-Cell Lymphoma: Biology, Diagnosis, and Management. The Oncologist 11:384-392.

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