Hemophagocytic Lymphohistiocytosis Secondary to T cell/histiocyte-rich Large B-cell Lymphoma

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Introduction:

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon disease that is often fatal when left untreated.[1] The diagnosis may be difficult due to the wide range of symptoms associated with HLH and the lack of specific diagnostic tests. HLH can be genetic or acquired. The inherited form is asscociated with mutations in genes that results in impaired function of natural killer cells and cytotoxic T cells.[2] The acquired form is often associated with infection, malignancy or autoimmune conditions. Hematologic neoplasms account for the majority of malignancy-associated HLH, and within this category, T-cell malignancies predominate. HLH associated with B-cell non-Hodgkin lymphoma is rare.[3]

Clinical History:

A 30-year-old male with a past medical history significant for adult-onset Still's disease diagnosed 1.5 years ago was transferred from an outside hospital with intermittent fever, jaundice, splenomegaly, pancytopenia, weight loss, and abnormal liver function tests. Labs were significant for elevated total bilirubin 10.2 mg/dL (0.3-1.2 mg/dL), alkaline phosphatase 410 IU/L (30-115 IU/L), AST 320 IU/L (10-41 IU/L), ALT 476 IU/L 10-40 IU/L), LDH 749 IU/L (110-240 IU/L), and ferritin 14298 ng/mL (23-336 IU/L). The patient's peripheral blood evaluation showed WBC 3,100/uL (4,300-10,300/uL), hemoglobin 10.9 g/dL (14.0-18.0 g/dL), and platelets 79,000 /uL (140,000-440,000/uL). An extensive infectious disease workup did not reveal an etiology. Concern for macrophage activation syndrome was raised on the basis of a markedly elevated ferritin in the context of fever and pancytopenia, and a bone marrow biopsy was performed.

Pathology:

Bone marrow aspirate smears were hemodilute but were notable for occasional macrophages exhibiting erythro- and leukophagocytosis (Fig. 1). Bone marrow biopsy demonstrated diffuse infiltration of the marrow space by lymphocytes and histiocytes, with a vaguely nodular pattern in some areas (Figs. 2A-C). Normal hematopoietic elements were not seen. The cellularity was composed predominantly of T cells with a cytotoxic phenotype (CD3, CD5, CD7, CD8, and TIA-1 +)(Figs. 3, 4). Admixed histiocytes (CD68+) were frequent (Fig. 4). CD20 highlighted scattered, large atypical cells (Fig. 4), that did not stain with CD15 or CD30. The bone marrow aspirate was hemodilute, and flow cytometry was again negative for an abnormal population.

Based upon the presence of hemophagocytic macrophages scattered among large, neoplastic B-cells and with a background of small, phenotypically normal cytotoxic T-cells, a diagnosis of hemophagocytic lymphohistiocytosis arising in a background of T cell/histiocyte-rich large B-cell lymphoma was made.

Clinical Follow-up:

The patient was treated first with targeted HLH therapy followed by targeted DLBCL therapy. He has achieved remission confirmed by clinical and laboratory workup, including follow-up bone marrow biopsy, and will be further consolidated with an autologous stem cell transplant.

Discussion:

The diagnosis of HLH can be difficult to make, but is important to recognize, as failure to initiate proper treatment can be fatal. Diagnostic criteria for HLH were updated in 2004 and rely on a combination of clinical, laboratory, bone marrow, and genetic results.[4] These include either a molecular diagnosis consistent with HLH (mutations in PRF1, UNC13D, STXBP2, RAB27A, STX11, SH2D1A, or XIAP), or the presence of 5 of the following 8 criteria: 1) fever; 2) splenomegaly; 3) two or more cytopenias; 4) hypertriglyceridemia and/or hypofibrinogenemia; 5) documented hemophagocytosis of bone marrow, lymph node or spleen; 6) low or absent natural killer cell activity; 7) elevated ferritin; 8) elevated soluble CD25 (IL-2 receptor)[4]. It has also been shown that an extremely elevated ferritin (>10,000 ug/L) is both sensitive (90%) and specific (96%) for the diagnosis of HLH.[5]

Further laboratory workup of our patient revealed hypertriglyceridemia (1040 mg/dL; reference range <150 mg/dL), hypofibrinogenemia (113.0 mg/dL; 150-400 mg/dL), and elevated soluble IL-2 receptor (7469 U/mL; 45-1105 U/mL). NK cell function was within normal limits. Thus, this patient fulfilled 7 out of 8 criteria for the diagnosis of HLH. Primary HLH was considered unlikely given the patient's age, and additional studies on peripheral blood did not show any abnormalities in expression of perforin, granzyme B, SLAM-associated protein, or X-linked inhibitor of apoptosis.

Studies of genetic HLH have shed light on the pathophysiology of the disease. It is thought that defects in cytotoxic pathways of T cells and NK cells can lead to an inability to clear antigenic stimuli, resulting in a "cytokine storm" and perpetuation of the inflammatory response.[1] Macrophage activation, hemophagocytosis, and tissue infiltration ensue. Genetic syndromes associated with HLH include familial HLH (associated with mutations in PRF1, UNC13D, STX11, STXBP2), Chediak-Higashi syndrome (associated with mutations in LYST), Griscelli syndrome (associated with mutations in RAB27A), Hermansky-Pudlak syndrome (associated with mutations in HPS-2), and X-linked proliferative syndrome (associated with mutations in XIAP). Each of these syndromes is associated with defective pathways of perforin and granule exocytosis from T cells and NK cells.[6]

Acquired HLH is most often associated with infections (49%), of which Epstein Barr virus is most common, followed by malignancies (27%), rheumatologic disorders (7%) and immune deficiency syndromes (6%).[1] When associated with malignancy, T and NK cell leukemias/lymphomas predominate, though it has also been seen with anaplastic large cell lymphoma, other leukemias, and solid tumors.

When associated with an autoimmune disease, the term "macrophage activation syndrome," or MAS, is used. Still's disease, also known as systemic-onset juvenile idiopathic arthritis, is a form of juvenile rheumatoid arthritis and carries an overall risk of MAS of 10%.[7] Lymphadenopathy is present in 60% of patients with Still's disease, and non-Hodgkin lymphoma has been reported as a rare complication.[8]

T cell/histiocyte-rich large B cell lymphoma (THRLBCL) accounts for <10% of DLBCL, and presents more commonly in males, with a median age of 30.[9] Splenic and extranodal involvement by the tumor is frequent. The diagnosis of THRLBCL is based on the identification of large neoplastic B cells comprising <10% of the overall cellularity in a background of phenotypically normal T cells and histiocytes.[10] The T cells with a cytotoxic phenotype predominate.[10]

Immunohistochemistry can assist with differentiation from classical Hodgkin lymphoma and from nodular lymphocyte-predominant Hodgkin lymphoma by demonstrating the presence of pan-B cell markers and absence of CD15 and CD30 on the large, neoplastic B-cells, and by demonstrating the presence of frequent T-cells and histiocytes in a diffuse growth pattern and the absence of an expanded network of follicular dendritic cells, respectively.

In retrospect, this patient had two risk factors for the development of acquired HLH: an autoimmune condition and a hematologic malignancy. The relationship between these two phenomena is unclear. However, we find it physiologically interesting that the diagnosis of THRLBCL was made with HLH in this case. While B-cell lymphomas are rarely encountered with HLH, defects in cytotoxic T and NK cell signaling are known to play a role in the pathophysiology of the disease. In this subtype of DLBCL, however, the predominant cell population consists of cytotoxic T cells, and we hypothesize that it is these T cells that may have incited a “cytokine storm”, leading to HLH.

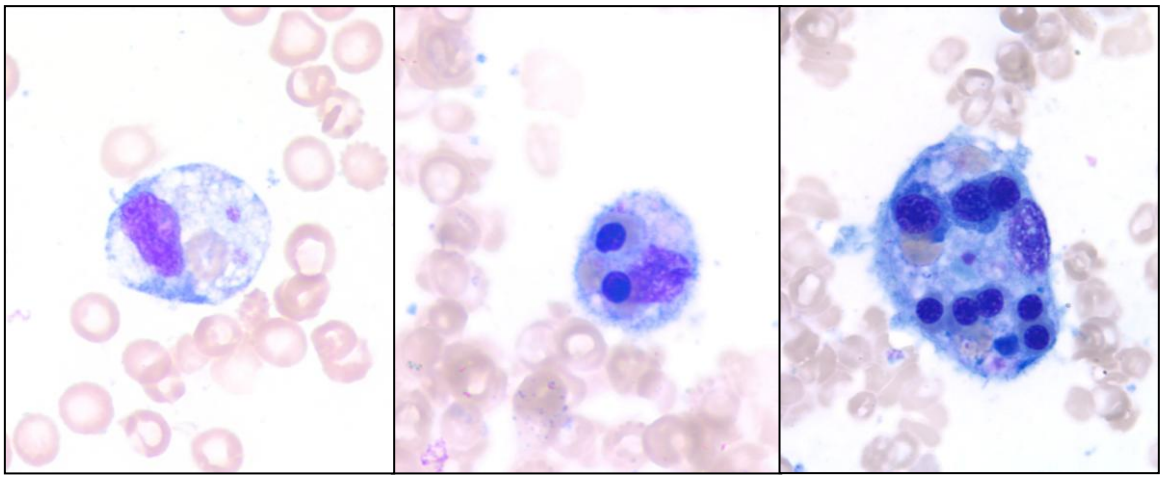

Figure 1: Three examples of macrophages showing hemophagocytosis, Wright-Giemsa, 1000x

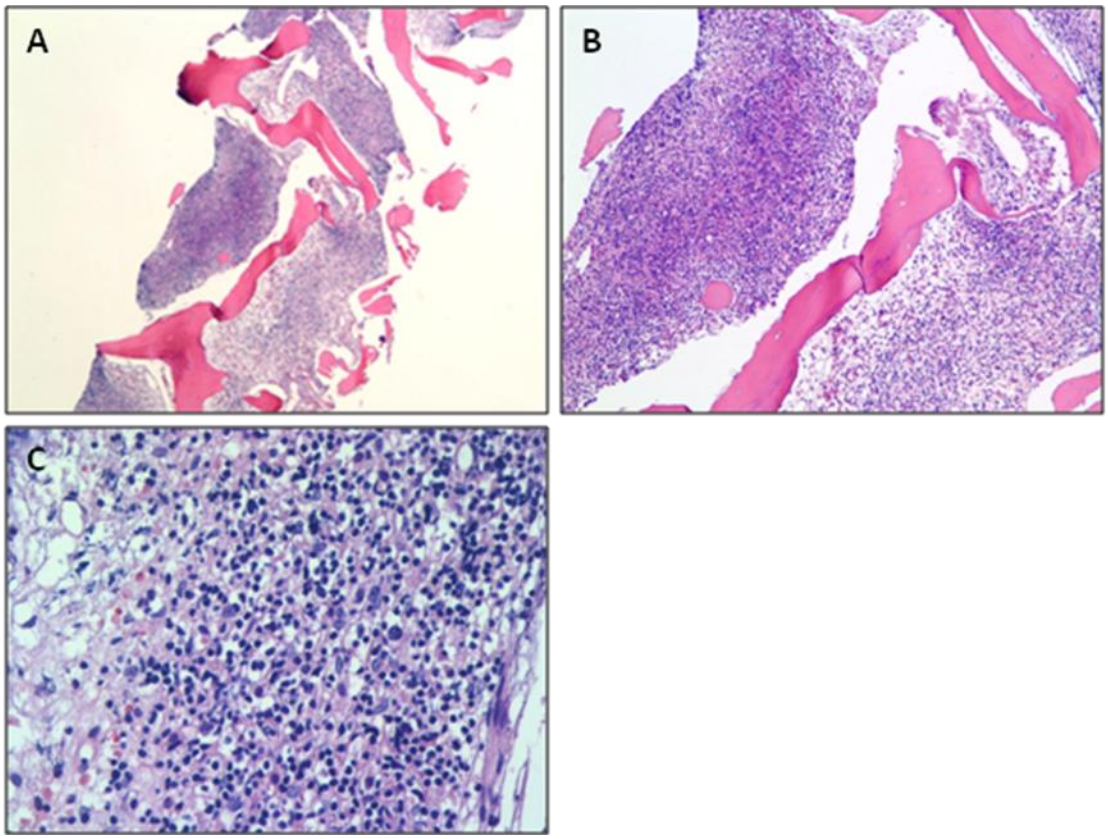

Figure 2A-C: Bone marrow biopsy showing a dense lymphoid infiltrate replacing hematopoietic marrow, with scattered large cells amidst a background of smaller cells, Hematoxylin & Eosin, (A)40x; (B)100x; (C)400x.

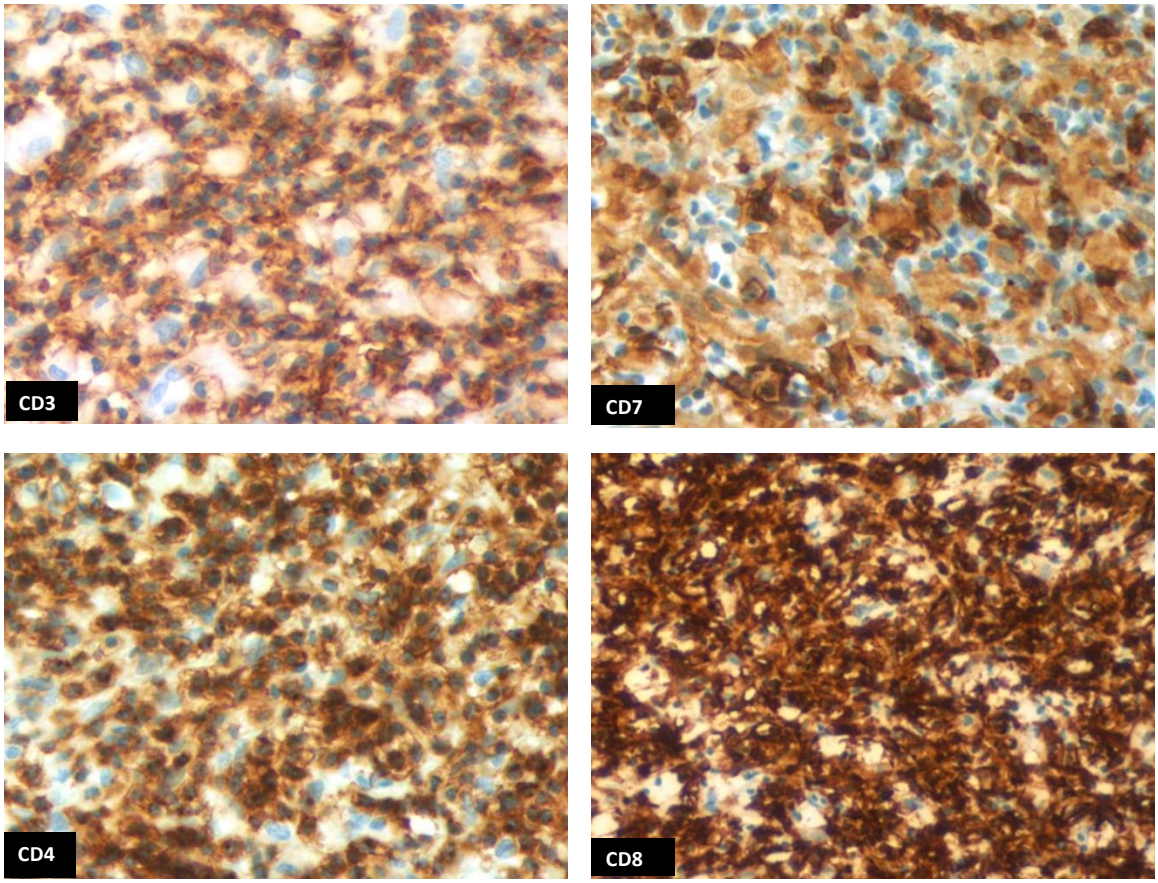

Figure 3: Immunohistochemical staining of the bone marrow biopsy with antibodies directed against CD3, CD7, CD4, and CD8, as indicated, 400x.

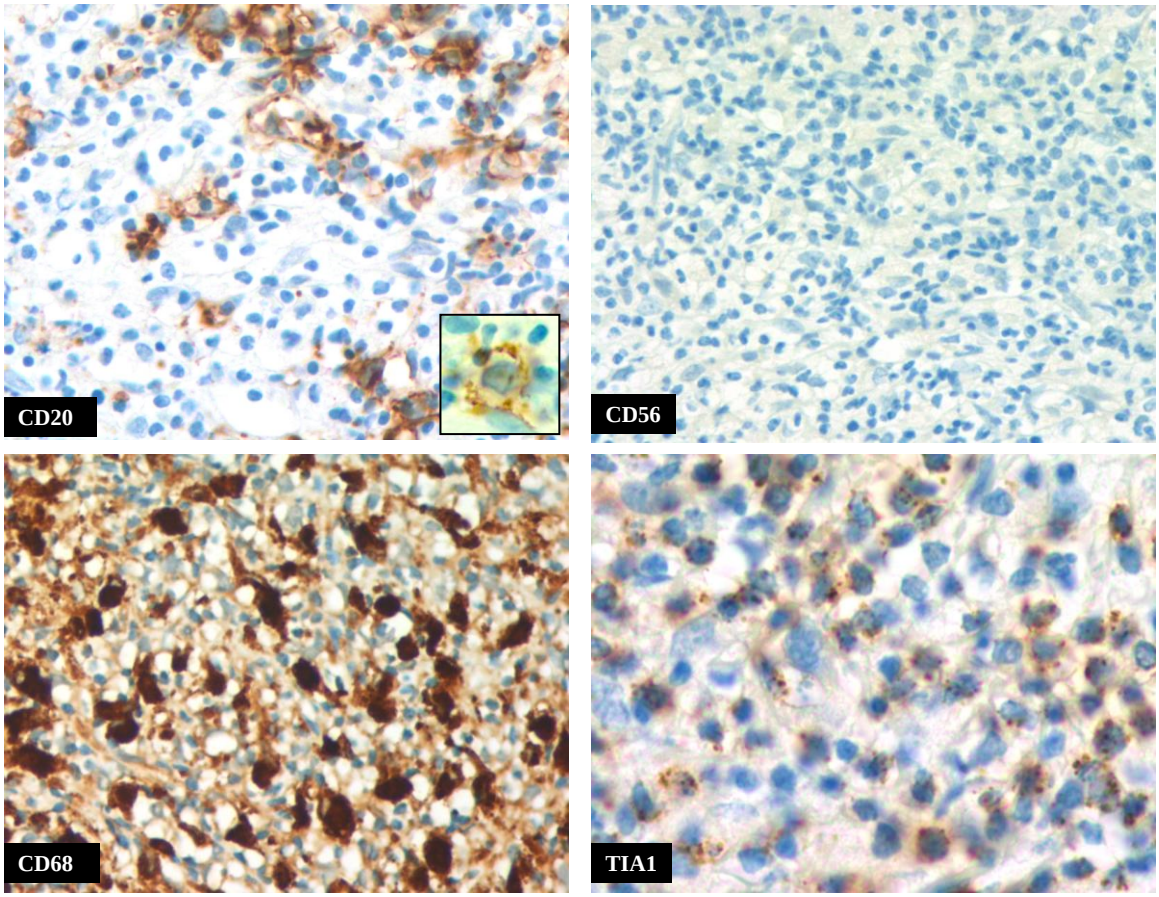

Figure 4. Immunohistochemical staining of the bone marrow biopsy with antibodies directed against CD20 (high power image, 1000x, inset), CD56, CD68, as indicated, 400x, and TIA1, 1000x.

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