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Seasonal fever for 11 years! A presentation of hemophagocytic lymphohistiocytosis secondary to marginal zone lymphoma

Abhishek Chaturvedi · Muhammad Salman Faisal · Ahmed Khattab · Joan Devine · Prerna Mewawalla

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Summary Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive inflammation and immune activation. The syndrome can be triggered by multiple events that disrupt immune homeostasis, including infection, autoimmune diseases, and lymphoma. Although more common in children—which might indicate a genetic cause—HLH can occur in patients of any age. The most common presenting features of HLH are fever, cytopenia, hepatitis, and splenomegaly. Other features include neurologic abnormalities such as altered mental status, seizures, and ataxia. It is a reactive process of antigen-presenting macrophages and $CD8^+$ T-cell activation and migration. In addition, abnormalities in the action or number of natural killer cells have been observed. Direct cytotoxicity from T cells, along with elevated levels of pro-inflammatory cytokines and interleukins, plays a role in the generation of excessive inflammation that leads to organ dysfunction. We present the case of a 61-year-old female patient with a past history of recurrent self-limiting episodes of fever that occurred two to three times every autumn for the past 11 years. The meticulous thought process that led to her diagnosis with HLH and marginal zone lymphoma is discussed.

Keywords Hemophagocytic lymphohistiocytosis · Marginal zone lymphoma · Fever · Immune dysregulation · Ferritin

A. Chaturvedi, MD · M. S. Faisal, MD (✉) · A. Khattab, MD · J. Devine, MD
Department of Internal Medicine, Allegheny Health Network, 320 East north Avenue, Pittsburgh, PA 15212, USA
Muhammad.faisal@ahn.org

A. Chaturvedi, MD
Abhishek.chaturvedi2@ahn.org

A. Khattab, MD
Ahmad.khattab@ahn.org

J. Devine, MD
Joan.devine@ahn.org

Dr. P. Mewawalla, MD
Department of Hematology/Oncology, Allegheny Health Network, 4800 Friendship Avenue, Pittsburgh, PA 15224, USA
Prerna.mewawalla@ahn.org

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive inflammation and immune activation. HLH can be triggered by multiple events that disrupt the immune homeostasis, including infection, autoimmune diseases, and lymphoma. We present the case of a 61-year-old female patient who presented with altered mental status and an 11-year history of seasonal fevers. The process that led to her diagnosis with HLH and the appropriate treatment response is discussed.

Case report

A 61-year-old female patient with a past medical history of Raynaud's phenomenon and recurrent febrile episodes for 11 years presented with altered mental status, fever, and gastrointestinal upset. In autumn every year, she had self-limiting episodes starting with cold symptoms, including a sore throat, runny nose, and cough. Following these symptoms, she developed intermittent spiking fevers as high as 103–105 °F (39.4–40.5 °C) along with vomiting and diarrhea. She associated all the episodes with a trip to Puerto Rico 11 years previously; she had the first episode after this trip. Her state of health during summer and spring is always normal. The only significant factor in her family history is systemic lupus erythematosus in her

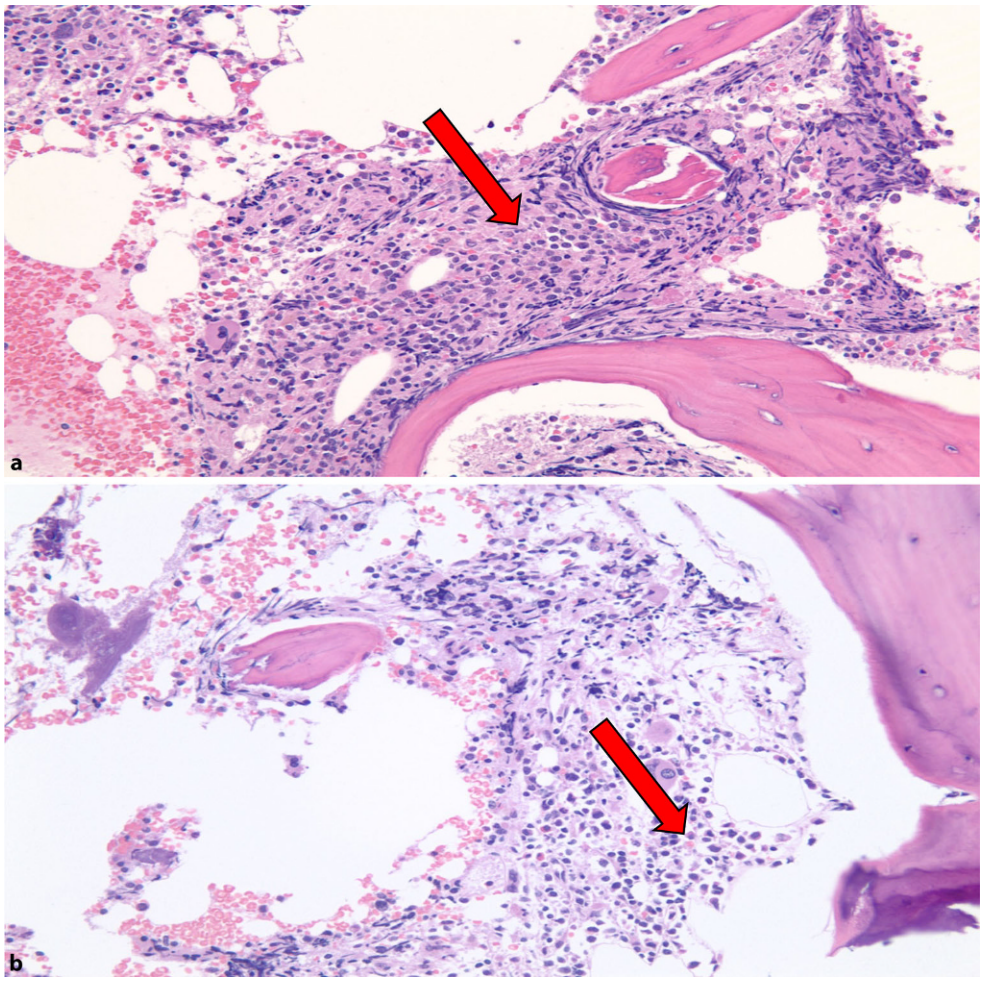


Fig. 1 Bone marrow biopsy showing atypical lymphoid proliferation and loss of normal hematopoietic elements. **a**, **b** Two views of bone marrow biopsy showing atypical lymphocyte proliferation (*red arrows*)

sister. She previously underwent extensive work-ups for potential etiologies performed by gastroenterologists, rheumatologists, and infectious disease specialists; the results remained negative. During admission to our institute, she appeared lethargic, icteric, and had a macular rash over her cheeks and a morbilliform rash over her chest and the back of her legs. She denied any recent tick bites. Laboratory work showed hemoglobin 11.5 g/dl, white blood cell count 2300/uL, platelets 45 k/mcl, lactic acid 6 mg/dl, total bilirubin 6.9 mg/dl, lactate dehydrogenase 391 U/dl, C-reactive protein 18 mg/dl, erythrocyte sedimentation rate 61 mm/h, and ferritin 1786 U/dl; urine analysis showed red blood cell (RBC) casts. Computed tomography (CT) of the head did not show any acute abnormality, while CT of the abdomen showed prominent mesenteric and retroperitoneal lymph nodes (LN). The initial differential diagnosis was broad and included infectious (meningitis, Lyme disease, malaria, anaplasmosis, hepatitis, cryptococcosis, Human Immunodeficiency Virus (HIV), Ebstein Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), parvovirus B19, adenovirus, respiratory viruses), autoimmune (lupus, connective tissue diseases, Still's disease, familial mediterranean fever (FMF), cryopyrin-associated disease, Whipple's disease), and hematological diseases. A lumbar puncture was performed, and blood cultures were obtained. The patient was then started on broad-spectrum antibiotics and relevant specialists were consulted. Further work-ups included antinuclear antigen (ANA), anti Sjogren's syndrome related antigen A (anti-SSA), anti Sjogren's syndrome related antigen B (anti-SSB), anti ribonucleoprotein antibody (anti-RNP), rheumatoid factor (RA factor), and anti cyclic citrullinated peptide antibody (anti-CCP). The AVISE® connective tissue disease panel was negative. The infectious disease work-up included CSF antigens for *S. pneumoniae, H. influenzae, N. meningitidis, E. coli,* Lyme disease, West Nile virus, and herpes simplex virus 1 and 2. All tested negative. Antistreptolysin O, CMV DNA, EBV DNA, Parvovirus B19 antibodies, adenovirus antibodies, and hepatitis C antibodies were all negative. Interestingly, a chest CT was obtained to look for thoracic lymphadenopathy and indicated that the patient had mild hepatosplenomegaly. Given the otherwise unremarkable work-ups, but abnormal laboratory findings, HLH was considered as differential diagnosis, and soluble Interleukin 2 receptor (IL2R) and triglycerides

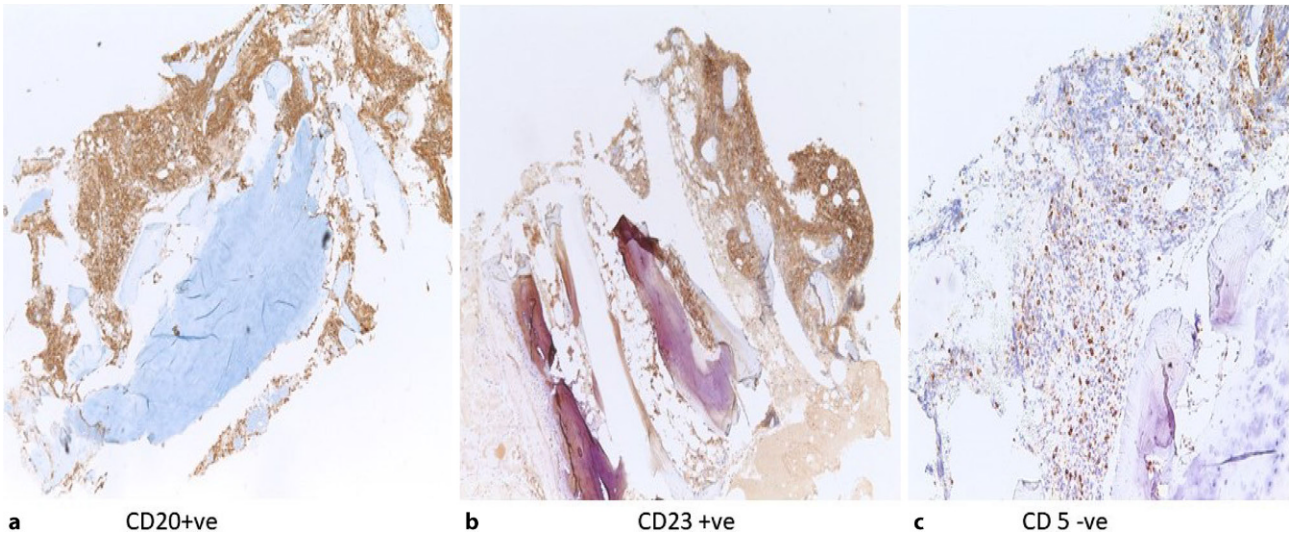
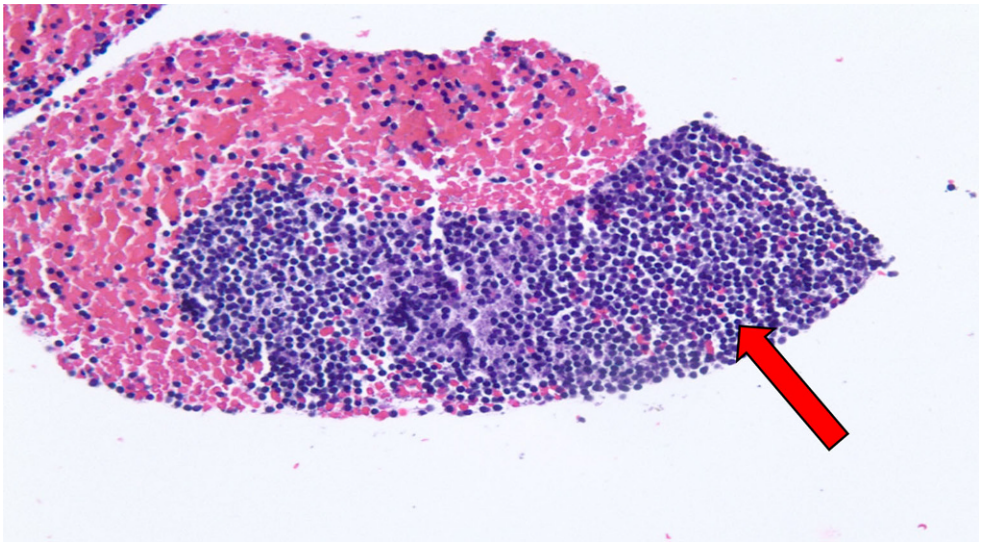


Fig. 2 Immunostaining of bone marrow biopsy showing positive staining for CD20 (**a**) and CD23 (**b**) and negative staining for CD5 (**c**)

Fig. 3 Lymph node biopsy showing uniform population of lymphoid cells with pale cytoplasm (*arrow*)



were ordered. Her soluble IL2R level was elevated to 7731 U/ml. Triglycerides were 338 mg/dl. Given the positive laboratory findings, including pancytopenia, elevated ferritin, triglycerides, soluble IL2R, splenomegaly, and fever, she was diagnosed with HLH. The patient underwent bone marrow (BM) and periportal LN biopsy, and she was started on dexamethasone 20 mg IV daily. Her mental status improved on the next day. The BM biopsy revealed a nodular and diffuse infiltrate of mature CD5/CD10/BRAF-negative B-lymphoproliferative cells (Fig. 1). Immunostaining was positive for CD19, CD20, CD45, CD23, and CD79, but negative for CD5, CD10, bcl2, CD56, and BRAF (Fig. 2). No hemophagocytes were seen. Lymph node biopsy showed atypical lymphoid proliferation consistent with marginal zone lymphoma (MZL; Fig. 3). Flow cytometry demonstrated B cell predominance with kappa light chain restriction. The immunophenotype was $CD19^{+}$, $CD20^{+}$, $CD22^{+}$, $CD5^{-}$, and $CD10^{-}$. She was discharged on outpatient steroid taper and started on chemotherapy with Rituximab as an outpatient. She has completed four cycles of rituximab. A repeat CT scan of her chest, abdomen, and pelvis was done 6 months after completion of treatment; the scan showed complete resolution of lymphadenopathy and a normal-sized spleen and liver. A repeat BM biopsy was done after completion of treatment, and did not show residual MZL. Flow cytometry did not show any evidence of lymphoproliferative disorder. The patient is followed up at the oncology clinic and was still in remission at her last clinic appointment.

Table 1 Diagnostic criteria for HLH

Fever, typically persistent daily
Splenomegaly
Bicytopenia: Hb < 9 g/dl, platelets <100,000/ul, neutrophils $<10^9$/l
Hypertriglyceridemia and/or hypofibrinogenemia
Hemophagocytosis in BM, spleen, LN, or CSF
Low or absent NK function (note: only present in approximately 50% of HLH patients)
Elevated ferritin (>500 mg/l) [15]
Soluble CD25 (IL2Ra) above normal limits for age [16]
Diagnosis on the basis of molecular findings consistent with HLH or at least five of the eight criteria listed here

BM bone marrow, *CSF* cerebrospinal fluid, *HLH* hemophagocytic lymphohistiocytosis, *LN* lymph node, *NK* natural killer

Discussion

Hemophagocytic lymphohistiocytosis is a syndrome of excessive inflammation that can be triggered by multiple events that disrupt the immune homeostasis. The common triggers are infection, autoimmune diseases, and lymphoma [1]. The syndrome involves uncontrolled activation and migration of antigen-presenting macrophages and $CD8^+$ T cells [2–4]. The most common presenting features of HLH are fever, cytopenia, hepatitis, and splenomegaly [1]. Neurologic abnormalities, including altered mental status, seizures, and ataxia can also be present. T-cell-mediated direct cytotoxicity and elevated levels of pro-inflammatory cytokines interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukins (IL) IL-6, IL-10, and IL-12, and the soluble IL-2 receptor (CD25) lead to excessive inflammation and result in organ dysfunction [5, 6]. The diagnostic criteria for HLH are presented in Table 1 [7].

The differential diagnosis of HLH is broad and includes rheumatologic diseases like adult-onset Still's disease, rheumatoid arthritis, systemic lupus erythematosus, familial Mediterranean fever, myeloid or lymphoid neoplasia, and infections such as febrile viral illnesses. Hemophagocytic lymphohistiocytosis has been reported in association with malignancies—most commonly lymphoid cancers—including leukemias and T-, NK-, and anaplastic large cell lymphomas. B-cell lymphoblastic leukemia, myeloid malignancies, and solid tumors occurring in association with HLH have also been noted [8, 9].

The association of lymphoma with HLH has been well documented in the literature [9–11]. Although HLH is more commonly related to T-cell lymphoma, in which HLH is more aggressive and fatal, it can occur in B-cell lymphomas [11, 12]. In a single-institute study of 57 patients with lymphoma who presented with HLH, 14 had B-cell lymphoma, while 43 had T-cell/NK-lymphoma [10]. The prognosis is poor for patients with aggressive lymphoma. Han et al. investigated 29 patients with HLH and aggressive lymphoma and found that the overall survival time for these patients was only 36 days [12]. However, in a case series of 30 patients with lymphoma-associated HLH, in which 17 patients had T-cell lymphoma and 13 patients had B-cell lymphoma, the median survival time for patients with B-cell lymphoma was much longer than for those with T-cell lymphoma (330 days vs. 96 days respectively). This result was, however, not statistically significant [13]. The most common B-cell lymphoma in the case series was diffuse large B-cell lymphoma, which is more aggressive than the MZL diagnosed in our patient.

The goal of HLH treatment is to suppress the excessive inflammation by dexamethasone and etoposide induction according to the HLH94 protocol. Intrathecal methotrexate is given to patients who present with central nervous system diseases. Maintenance therapy is with dexamethasone and intrathecal methotrexate [14]. In 2004, a new experimental protocol for treatment of HLH was started, which emphasizes treatment with cyclosporine early in induction. In lymphoma-associated HLH, treatment regimens that include chemotherapy are known to improve outcomes [10]. Patients with B-cell lymphoma that are treated with rituximab have a better long-term prognosis [13].

Conflict of interest A. Chaturvedi, M.S. Faisal, A. Khattab, J. Devine, and P. Mewawalla declare that they have no competing interests.

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