

CLINICAL VIGNETTE

A Case of Hemophagocytic Lymphohistiocytosis

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Case Presentation

A 31-year-old man presented to the emergency department (ED) from an outside hospital with fever, pancytopenia and liver failure. Three months prior, he developed right foot swelling, which progressed into an erythematous, macular, and pruritic rash. The rash had extended proximally and involved his contralateral leg, arms, and torso. At an outside ED, he was treated for cellulitis with trimethoprim/sulfamethoxazole and cephalexin. The initial rash site resolved, but rashes elsewhere on his body were increasingly pruritic. He was admitted at an outside hospital for fever, mild pancytopenia, and elevated liver chemistries. He was treated with high dose corticosteroids for a presumed drug reaction. Though the rash resolved, he continued to have intermittent fevers despite a negative infectious work up. Upon completion of the

corticosteroid taper, he developed a high-grade fever with a maximum of 39.4°C. He was re-admitted to the same hospital and found to have worsened pancytopenia and elevated liver chemistries. Ferritin level was notably elevated to 14,133 ng/mL. Infectious workup was negative, and bone marrow biopsy was unrevealing. A computed tomography (CT) scan of the chest, abdomen, and pelvis showed nodules in the right and left lower lobes, retroperitoneal lymphadenopathy in the right pelvis, diffuse hypodense liver nodules, and numerous splenic masses. Lymph node biopsy was non-diagnostic showing necrotic tissue. Liver biopsy demonstrated no infectious or malignant process. He was treated for febrile neutropenia with the working diagnosis of drug-induced agranulocytosis. He developed anasarca and

jaundice. He left the outside hospital and presented to our ED for further evaluation.

The patient had previously enjoyed good health. His past medical history was significant for an allergic rash to amoxicillin as a child. He took no medications. Social history was remarkable for use of adulterated cocaine. He worked as a visual effects specialist. His family history was unremarkable.

He was afebrile and tachypneic with other vital signs stable. He was alert and oriented and in moderate discomfort from the anasarca. Physical examination was notable for scleral and frenular icterus, marked abdominal ascites, 3+ pitting edema in the lower extremities, jaundice, and no rashes. Diagnostic testing on admission was remarkable for a white blood cell count of $1.83 \times 10^3/\mu\text{L}$, hemoglobin of 7.6 g/dL, platelet of $52 \times 10^3/\mu\text{L}$, alkaline phosphatase of 454 U/L, aspartate aminotransferase of 652 U/L, alanine aminotransferase of 534

U/L, direct bilirubin of 10.4 mg/dL, total bilirubin of 18.7 mg/dL, fibrinogen of 78 mg/dL, ferritin >20,000 ng/mL, triglyceride 402 mg/dL, PTT 46.2 seconds, PT 13.3 seconds, INR 1.3, and lactate dehydrogenase 1154 U/L.

On subsequent days, he continued to have fevers to 38.5°C. A thorough workup for infectious and rheumatologic etiologies was negative. CT showed hepatosplenomegaly with findings similar to prior. Laparoscopic omental, liver, and peritoneal biopsy and CT-guided biopsy of retroperitoneal lymph nodes were non-diagnostic showing only necrotic tissue (Figure 1). Due to a high suspicion for hemophagocytic lymphohistiocytosis (HLH) based on fulfillment of diagnostic criteria and considering the high mortality from delayed treatment, the diagnosis was made on clinical grounds despite absent tissue evidence. A protocol consisting of dexamethasone, etoposide, and cyclosporine was initiated on hospital day three. The

patient became afebrile but remained pancytopenic. Repeat CT of the abdomen showed decreased size of the retroperitoneal lymph nodes. A bone marrow biopsy 11 days after initiation of treatment revealed a markedly hypocellular marrow with numerous histiocytes, some showing hemophagocytosis (Figure 2). The patient's hospital course was complicated by acute liver failure, acute renal failure, vancomycin-resistant enterococcus bacteremia, gastrointestinal bleed, respiratory failure secondary to herpes simplex virus and aspergillus pneumonia, narrowing of the bilateral iliac and renal arteries due to vasculitis, and coagulopathy. The patient developed septic shock and chemotherapy was discontinued. Given that the patient had a history of adulterated cocaine use, the diagnosis of drug-induced vasculitis as a trigger for HLH was postulated pending autopsy findings. Despite full supportive care, the patient developed multi-organ failure and expired.

Discussion

HLH is a rare hyperinflammatory disease with typical clinical findings of fever, cytopenia, and hepatosplenomegaly that should be considered in patients with unexplained multi-organ failure.¹

There are two different forms of HLH that may be difficult to distinguish: 1) primary HLH, and 2) secondary HLH (sHLH).^{1,2} Primary HLH can be further divided into 2 subgroups. One subgroup, known as familial hemophagocytic lymphohistiocytosis (FHLH) typically manifests in the first year of life.³ The second subgroup consist of immune deficiency syndromes that sometimes are associated with HLH, such as Chediak-Higashi syndrome, Griscelli syndrome, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, severe combined immunodeficiency, lysinuric protein intolerance, and Hermansky-Pudlak syndrome.³ In contrast, FHLH is an autosomal recessive disease with an incidence of 1:50,000 live-born children.⁴ It

is associated with a number of mutations, notably in either the perforin gene, causing a defect in Natural Killer (NK) cell and T cell cytotoxicity, or in the hMunc gene, causing a defect in the function of cytolytic granules.¹ Once thought of as a pediatric disease, FHLH can present at any time in life.⁵

Secondary HLH may be caused by an immunologic reaction to viral, bacterial, or parasitic infections or from rheumatologic or malignancies such as lymphomas.¹ Viruses associated with HLH include herpes virus (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, and human herpesvirus 8), HIV, adenovirus, hepatitis viruses, parvovirus, and influenza.³ Bacterial causes can include mycobacteria and spirochetes.³ Rheumatologic etiologies include systemic lupus erythematosus, Still's disease, rheumatoid arthritis, sarcoidosis, scleroderma, mixed connective tissue disease, and Sjogren's syndrome.⁶ Although HLH can be thought of as two separate

conditions, they are hard to distinguish clinically. Once an infectious etiology is found, it does not preclude the diagnosis of FHLH, because both FHLH and sHLH can have infectious triggers. Generally, FHLH occurs more frequently than sHLH.⁶

The multi-system inflammation caused by HLH is due to a cytokine storm. Patients have elevated levels of interleukin (IL) 1- β , tumor necrosis factor (TNF) α , IL-6, and IL-8.⁵ The uncontrolled activity of histiocytes and T-cells cause elevated cytokine levels, which produce organ damage.

Manifestations of HLH can be explained by cytokine damage to organs. Cytopenia is a result of hemophagocytosis in the bone marrow (the histiologic finding of histiocytes phagocytizing red blood cells) and a result of interferon- γ (IFN- γ), TNF- α , and IL-1 β suppressing hematopoiesis.⁶ Thrombocytopenia typically occurs earlier in the disease course than leukopenia and with greater reduction in value. Colony-

stimulating factor (CSF) and Fas/Fas-ligand interaction results in liver damage, leading to coagulopathy with hypofibrinogenemia, both of which are common in HLH patients.⁶ In advanced HLH, renal failure is due to IL-6 with damage to the glomerulus. Hyperferritinemia is due to IL-1 β , and hypertriglyceridaemia is secondary to TNF- α inhibition of lipoprotein lipase.^{7,8}

Although there are various forms of HLH, the clinical presentations are similar. Prolonged fevers and hepatosplenomegaly are cardinal symptoms. The patient may have ataxia and seizures at initial presentation and can develop hypo or hypertonia, cranial nerve palsies, or signs of increased intracranial pressure.⁵ Less frequent are lymphadenopathy, rash, and diarrhea.⁴ Lab values will be notable for cytopenias, hypofibrinogenemia, hypoalbuminemia, hyponatremia, hypertriglyceridemia, hyperferritinemia, elevated liver transaminases, and elevated alpha chain of the soluble IL-2 receptor

(sCD25).^{5,9} Very elevated levels of the alpha chain of sCD25 is specific for HLH as it is not usually seen in other diseases.⁵ NK function is low or absent in most patients, but NK cell number may be preserved.⁵ During the early course of HLH, bone marrow biopsy may not show hemophagocytosis, and liver biopsy may also be unrevealing showing only perivascular lymphoid infiltrates.⁵

The Histiocyte Society developed diagnostic guidelines in 2004 based on clinical, laboratory, and histopathologic criteria (Table 1).

The treatment protocol is based on the 2004 guidelines from the Histiocyte Society. There is an initial and continuation therapy protocol consisting of dexamethasone, etoposide, and cyclosporine A. Methotrexate and prednisolone may be added if neurologic symptoms progress.¹ During continuation therapy, the patient should undergo stem cell transplantation.

In summary, HLH is a rare diagnosis that should be considered in the setting of unexplained multi-organ failure with fever, cytopenia, and hepatosplenomegaly. Early

recognition is important because HLH has a high mortality and early treatment may be more effective.

FIGURES AND TABLES:

Figure 1. Laparoscopic view of the liver showing areas of necrosis.



Figure 2. Bone marrow biopsy. The decalcified subcortical bone marrow biopsy section showed a hypocellular marrow with an approximate cellularity of 10%. Histiocytes have largely replaced the normal marrow elements, with some histiocytes showing hemophagocytosis (black arrow). The hematopoietic density is <5%. No other focal lesions were noted.

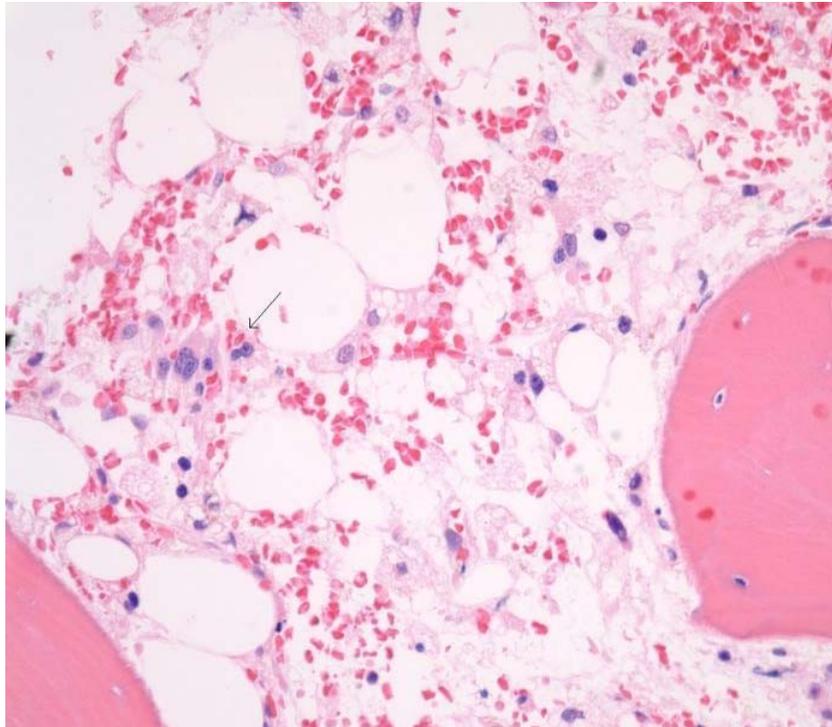


Table 1. Diagnostic guidelines for HLH

<p>The diagnosis of HLH is established if either 1 or 2 below is fulfilled:</p> <ol style="list-style-type: none">1. A molecular diagnosis2. Having 5 out of 8 criteria fulfilled:<ol style="list-style-type: none">a. Feverb. Splenomegalyc. Cytopenia (affecting ≥ 2 cell lineages): hemoglobin ≤ 9 g/dL, platelets $<100,000/\mu\text{L}$, or neutrophils <1000 cells/μLd. Hypertriglyceridaemia (fasting triglyceride ≥ 265 mg/dL) and/or hypofibrinogenaemia (fibrinogen ≤ 1.5 g/L)e. Hemophagocytosis in bone marrow, spleen, or lymph nodesf. No evidence of malignancyg. Hyperferritinaemia (ferritin ≥ 500 $\mu\text{g/L}$)h. Elevated soluble CD25 ≥ 2400 U/mL <p>Adapted from reference 8.</p>
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REFERENCES

1. *HLH 2004 Protocol.*
2. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. *HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis.* *Pediatr Blood Cancer.* 2007 Feb;48(2):124-31. PubMed PMID: 16937360.
3. Roupael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. *Infections associated with haemophagocytic syndrome.* *Lancet Infect Dis.* 2007 Dec;7(12):814-22. Review. PubMed PMID: 18045564.
4. Henter JI, Elinder G, Söder O, Ost A. *Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis.* *Acta Paediatr Scand.* 1991 Apr;80(4):428-35. PubMed PMID: 2058392.
5. Filipovich AH. *Hemophagocytic lymphohistiocytosis (HLH) and related disorders.* *Hematology Am Soc Hematol Educ Program.* 2009:127-31. PubMed PMID: 20008190.
6. Créput C, Galicier L, Buyse S, Azoulay E. *Understanding organ dysfunction in hemophagocytic lymphohistiocytosis.* *Intensive Care Med.* 2008 Jul;34(7):1177-87. Epub 2008 Apr 22. Review. PubMed PMID: 18427781.
7. Esumi N, Ikushima S, Hibi S, Todo S, Imashuku S. *High serum ferritin level as a marker of malignant histiocytosis and virus-associated hemophagocytic syndrome.* *Cancer.* 1988 May 15;61(10):2071-6. PubMed PMID: 3359404.
8. Henter JI, Carlson LA, Söder O, Nilsson-Ehle P, Elinder G. *Lipoprotein alterations and plasma lipoprotein lipase reduction in familial hemophagocytic lymphohistiocytosis.* *Acta Paediatr Scand.* 1991 Jun-Jul;80(6-7):675-81. PubMed PMID: 1867086.
9. Janka GE. *Hemophagocytic syndromes.* *Blood Rev.* 2007 Sep;21(5):245-53. Epub 2007 Jun 21. Review. PubMed PMID: 17590250.

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