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Case report Open Access

Hemophagocytic Lymphohistiocytosis Case Series

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Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening syndrome of excessive multisystem inflammation and tissue destruction due to abnormal immune activation. It is more frequently seen in the pediatric population, either as a genetic disorder or secondary to infection or autoimmune disease, but can present in acquired forms at any age. It is thought to be due to an absence of downregulation of activated macrophages by Natural Killer (NK) cells and/or cytotoxic lymphocytes. This then leads to excessive macrophage activity and results in cytokine storm and tissue damage [1-3].

Prompt diagnosis and initiation of treatment has improved survival [4-6]. However, due to the rarity of this disease, variable clinical presentation, and lack of specificity of clinical and lab findings, there is often a delay in diagnosis and thus treatment. The criteria for diagnosis of HLH is based on the presence of five (out of eight) criteria: fever (≥ 38.5°C), splenomegaly, cytopenias (at least two of the following: hemoglobin < 9 g/dL, platelets < 100,000/uL, or absolute neutrophil count <1000/uL), hypertriglyceridemia (fasting TG > 265 mg/dL) and/or hypofibrinogenemia (fibrinogen < 150 mg/dL), hemophagocytosis in bone marrow, spleen, lymph node or liver, low or absent NK cell activity, ferritin > 500 ng/mL, and elevated soluble CD25 two standard deviations above the norm [5]. In practice, among 249 cases of HLH in the HLH-94 study, the most common presentations were hepatomegaly (95%), lymphadenopathy (33%), neurologic symptoms (33%), and rash (31%) [4].

Three patients presented to our hospital recently with variable presentations, but all were found to have non-specific gastrointestinal or biliary tract inflammation on imaging and were eventually diagnosed with HLH. We discuss their courses here.

Case 1

A 69-year-old man was admitted for fever of unknown origin (FUO) for three months, fatigue, and dyspnea. Physical exam was notable for fever of 38.3°C decreased right lower lobe breath sounds and bilateral basilar crackles. Labs were notable for hyponatremia, transaminitis, leukocytosis (neutrophil predominance) and anemia. Chest radiography showed right lower lobe consolidation. He was empirically started on broad spectrum antibiotics to treat for pneumonia as well as a suspected intra-abdominal infection. An extensive infectious and malignant workup for FUO was unrevealing, but he was empirically treated for leptospirosis based on recent travel and exposure history in Hawaii. A repeat extensive infectious and malignant workup, including serum protein electrophoresis (SPEP), was again noncontributory. Computed Tomography Scan (CT) showed peripancreatic inflammation, non-pathologically enlarged retroperitoneal adenopathy, and stable subcentimeter nodules throughout the liver that likely represented cysts. Positron Emission Tomography (PET/CT) scan showed non-specific increased marrow and spleen uptake. Liver biopsy showed possible cholangitis, pericholangitis, portal edema and increased neutrophils within the sinusoids, though a Magnetic Resonance Cholangiopancreatography (MRCP) and abdominal ultrasound were negative. The patient did not have any abdominal symptoms throughout his admission. His ferritin was found to be elevated at 4,442 ng/mL. He later developed thrombocytopenia. During his course, he developed acute respiratory failure and was intubated; bronchoscopy with bronchoalveolar lavage (BAL) was negative for infection or malignancy. Initial bone marrow biopsy showed hypercellular marrow with trilineage hematopoiesis and myeloid hyperplasia. Peripheral blood smear showed neutrophilia with toxic changes, monocytosis, hypochromic microcytic anemia, and thrombocytopenia. A repeat bone marrow biopsy was later performed and showed scattered hemophagocytosis in addition to the previous findings, and CD25 levels returned elevated at 5,850 pg/mL. A diagnosis of HLH was made and he was started on etoposide with a dexamethasone taper. It was initially unclear why the patient had non-specific inflammation and adenopathy of the pancreas on CT as well as evidence of bile duct inflammation on liver biopsy as he had no abdominal complaints, but it was later felt to be secondary to the generalized multi-organ inflammatory process of HLH. Two weeks later the patient opted for hospice care and is still alive today.

Case 2

A 50-year-old woman with a history of lymphocytic gastroduodenitis was admitted for worsening diarrhea and failure to thrive. During her prolonged hospital course, she developed FUO. An esophagogastroduodenoscopy (EGD) and gastric biopsy showed H. pylori and she was started on triple therapy. During her hospital stay, she was empirically treated for possible culture negative endocarditis, Whipple's disease, and a suspected herpetic skin lesion, though an extensive infectious work up was eventually negative. On day 17 of hospitalization she developed pancytopenia, hyponatremia and transaminitis. Right upper quadrant ultrasound suggested acute cholecystitis, though she did not have abdominal pain. A follow up hepatobiliary iminodiacetic acid scan (HIDA) was normal. A CT scan of the abdomen showed gallstones, mild gallbladder and partial bowel wall thickening, non-specific pancreatic head fullness and ascites. Paracentesis was performed and ascitic fluid cultures were negative. An echocardiogram showed no vegetations. CT angiogram was normal. PET/CT scan showed a hypermetabolic soft tissue mass in the left abdomen that was suspicious for malignancy, but was unable to be biopsied given her unstable clinical status. An extensive rheumatologic

work up was unrevealing. Viral serology showed *Cytomegalovirus* (CMV) positivity with a high viral load and she was started on Ganciclovir. Antibodies to *Epstein Barr Virus* (EBV) were identified but no active infection was present as the quantitative polymerase chain reaction (PCR) testing was normal. She eventually developed acute hypoxemic respiratory failure and was intubated. Chest radiography demonstrated non-specific bilateral effusions and opacities. Bone marrow biopsy showed increased histiocytes with hemophagocytosis. Her ferritin was elevated at 19,423 ng/mL, fibrinogen was low at 56 mg/dL, and triglycerides were elevated at 660 mg/dL. CD25 levels were elevated at 16,910 pg/mL. She was diagnosed with HLH and was started on etoposide and dexamethasone. Though imaging showed gall bladder, bowel wall and pancreatic inflammation and edema, she lacked abdominal symptoms and it was felt that these non-specific findings were secondary to HLH. She was eventually discharged and re-admitted several times. Three months after her initial HLH diagnosis, she was re-admitted for severe sepsis. On hospital day 19 she had Pulseless Electrical Activity (PEA) arrest and was found to have a spontaneous intracranial hemorrhage related to her thrombocytopenia and coagulapathy with evidence of herniation; she was transitioned to comfort care and passed away on hospital day 20.

Case 3

A 69-year-old man with a history of diffuse large B-cell lymphoma (DLBCL) in remission, who completed treatment with chemotherapy and radiation presented with night sweats, weakness, weight loss and respiratory distress. On admission, he was found to be in shock with multi-organ failure. He was emergently intubated for respiratory failure. Labs revealed Disseminated Intravascular Coagulation (DIC), acute renal failure, transaminitis, leukocytosis, anemia and thrombocytopenia. His ferritin level was elevated at 17,000 ng/mL. CT scan of the abdomen and pelvis showed diffuse small bowel wall thickening, moderate splenomegaly, and non-specific pericholecystic and pancreatic infiltrates. Right upper quadrant ultrasound showed a mildly thickened gallbladder wall. However, he never had any abdominal complaints throughout his hospital stay. He was started on broad-spectrum antibiotics however subsequent infectious workup was unrevealing. The peripheral blood smear showed many large lymphocytes with clonality confirmed on flow cytometry; bone marrow biopsy revealed hemophagocytosis, concerning for lymphoma-induced HLH. He was started on chemotherapy for large B-cell lymphoma with rituxan, oxaliplatin and gemcitabine. He improved clinically after one cycle of chemotherapy and was discharged from the hospital. His CT and ultrasound findings of diffuse small bowel wall thickening, as well as pericholecystic and pancreatic inflammation, was felt to be secondary to his HLH. He remains alive 8 months later.

Discussion

HLH is a progressive, life threatening illness caused by excessive immune activation that requires vigilance on the part of the treating physicians to diagnose promptly and swiftly initiate treatment. Our three cases highlight the variable clinical presentations of HLH, though consistently seen as an acute illness with multi-organ involvement. Common among our patients was fever, sepsis, hepatosplenomegaly, neurologic decline, acute respiratory failure, hyponatremia, transaminitis, cytopenias, elevated ferritin and CD25 levels. Interestingly, all three patients in this series had gastrointestinal tract or biliary duct inflammation on imaging, although none had any abdominal symptoms. HLH is a syndrome of excessive and persistent macrophage and NK cell activity which eventually leads to cytokine storm, tissue destruction and multi-organ failure [7-10]. This process may account for the findings of gastrointestinal tract and biliary duct inflammation that was seen on imaging from our patients.

It is incumbent for clinicians who suspect HLH in a febrile patient with the constellation of splenomegaly, cytopenias, hemophagocytosis, hypertriglyceridemia, elevated ferritin and elevated soluble CD25 levels with low NK cell activity to initiate treatment rapidly as the reported mortality for untreated patients is extremely high. It is also important to recognize findings of gastrointestinal and biliary inflammation on imaging, as seen in our patients with HLH, as it may be an asymptomatic incidental finding likely secondary to this excessive inflammatory syndrome. Most experts recommend treatment based on HLH-94 protocol [4-6,9] that includes induction therapy with etoposide and dexamethasone as well as treating any underlying immunologic trigger. HLH carries a very poor prognosis, even with treatment, as our case series supports. More studies are needed to help understand, diagnose and optimize treatment for this uncommon and often fatal disease (Table 1).

Case	1	2	3
Fever > 38.5°C	+	+	+
Splenomegaly	+	-	+
Cytopenias	+	+	+
Hypertriglyceridemia (fasting TG > 265 mg/dL) and/or hypofibrinogenemia (fibrinogen < 150 mg/dL)	-	+	+
Hemophagocytosis on bone marrow biopsy	+	+	+
Elevated ferritin > 500 ng/mL	+	+	+
Low/absent NK-cell activity	N/A	N/A	N/A
Elevated soluble CD25 > 2 standard deviations above normal range	+	+	+
Presented with hyponatremia	+	+	+
Gastrointestinal/biliary inflammatory changes on imaging	+	+	+

Table 1: Summary of patient findings.

References

1. Filipovich A, McClain K, Grom A (2010) Histiocytic disorders: Recent insights into pathophysiology and practical guidelines. Biology of Blood and Marrow Transplantation 16: S82-S89.
2. Henter J, Elinder G, Soder O, Hansson M, Andersson B, et al. (1991) Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. Blood 78: 2918-2922.
3. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, et al. (1997) Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood 89: 4100-4103.
4. Trottestam H, Horne A, Aricò M, Egeler R, Filipovich A, et al. (2011) Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: Long-term results of the HLH-94 treatment protocol. Blood 118: 4577-4584.
5. Jordan MB, Allen CE, Weitzman S, Filipovich A, McClain KL (2011) How i treat hemophagocytic lymphohistiocytosis. Blood 118: 4041-4052.

6. Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, et al. (2002) Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 100: 2367-2373.
7. Imashuku S, Hibi S, Ohara T, Iwai A, Sako M, et al. (1999) Effective control of Epstein-Barr Virus–related hemophagocytic lymphohistiocytosis with immunochemotherapy. Blood 93: 1869-1874.
8. Schneider E, Lorenz I, Müller-Rosenberger M, Steinbach G, Kron M, et al. (2002) Hemophagocytic lymphohistiocytosis is associated with deficiencies of cellular cytolysis but normal expression of transcripts relevant to killer-cell-induced apoptosis. Blood 100: 2891-2898.
9. Schram A, Berliner N (2015) How i treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 125: 2908-2914.
10. Filipovich A (2009) Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Hematology ASH Education Program Book: 127-131.