A Rare and Fatal Case of Hemophagocytic Lymphohistiocytosis Associated with Sarcoidosis

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Patient: Male, 48-year-old
Final Diagnosis: Hemophagocytic lymphohistiocytosis
Symptoms: Abdominal pain • nausea • vomiting • weight loss
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Rare disease
Background: Sarcoidosis is a systemic inflammatory disorder characterized by a classic pathologic feature of non-caseating granulomas involving any organ system. Hemophagocytic lymphohistiocytosis (HLH) is a catastrophic cytokine surge characterized by dysregulation of the macrophage response, which can be rapidly fatal. Recognition of HLH has been increasing over the past decade. HLH can present with features of sepsis that can make the diagnosis challenging and requires high clinical suspicion.

Case Report: We report a case of a 48-year-old African American male with a past medical history of sarcoidosis infiltrating the lymph nodes, liver, and bone marrow with initial presentation of abdominal pain, nausea, vomiting, and weight loss of 100 pounds over 8 months. Sepsis was suspected, but the patient clinically deteriorated with vancomycin and cefepime. Fevers, bone marrow biopsy, anemia, thrombocytopenia, elevated ferritin, and elevated soluble receptor interleukin 2 confirmed HLH. The patient was treated with etoposide and dexamethasone with poor response and died from cardiac arrest.

Conclusions: Sarcoidosis associated with HLH is an extremely rare phenomenon with only 10 cases reported in the literature. Early clinical suspicion can be challenging as this condition is a sepsis-mimicker. To reduce mortality, prompt initiation of therapy is a key determinant in patients who are clinically deteriorating despite treatment for sepsis.

MeSH Keywords: Lymphohistiocytosis, Hemophagocytic • Macrophage Activation Syndrome • Sarcoidosis

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Background

Sarcoidosis is a chronic granulomatous disease predominantly affecting young African American females [1]. The mechanism of sarcoidosis is unknown. It is believed to be associated with an inappropriate T cell-mediated immune response [1]. Hemophagocytic Lymphohistiocytosis (HLH) is a rare and fatal diagnosis. It occurs as a result of rapidly fatal proliferation of histiocytes with subsequent hemophagocytosis, which leads to a severe hyperinflammatory response. HLH can occur as a primary disease, which is caused by genetic defects. Secondary HLH can result from rheumatologic, infectious, or malignant etiologies. The key manifestations of HLH are hepatosplenomegaly, fever, and progressive cytopenias. Mortality rates range from 8% to 22% [2]. There have been few case reports describing the relationship between sarcoidosis and HLH [3]. The relationship between sarcoidosis and HLH includes and inflammatory cascade with a resulting “cytokine storm” [1]. Some patients with sarcoidosis have a higher number of monocytes with more HLA markers and adhesion molecules [1]. We present an extremely rare case of a patient with a known history of sarcoidosis who developed HLH unresponsive to aggressive treatment.

Case Report

A 48-year-old incarcerated male presented to an outside hospital with a 2-month history of multisystem sarcoidosis involving the bone marrow, liver, and lymph nodes (Figures 1–3) diagnosed with biopsy showing non-caseating granulomas. The patient’s chief complaint consisted of an 8-month history of progressive abdominal pain, 100-pound weight loss, nausea, and vomiting. His other medical history was significant for paraplegia with urinary retention (due to a motor vehicle accident 6 years prior), asthma, type 2 diabetes mellitus, gastroesophageal reflux disease, hiatal hernia, hypertension, and alcoholism. The patient had magnetic resonance imaging (MRI) of the thoracic spine 3 years prior that showed no evidence of central spinal canal stenosis or spinal compression. There were findings of degenerative disc disease of the thoracic spine. The patient also had an MRI of the lumbar spine 3 years prior that showed disc bulging at L5–S1 with no cord compression. His home medications included albuterol, terazosin, oxybutynin, and pantoprazole. He was admitted to an outside hospital 2 months prior to his initial presentation, where he was diagnosed with sarcoidosis with manifestations of weight loss and abdominal pain. He was found to have leukopenia and anemia. Computed tomography (CT) abdomen and pelvis revealed large mesenteric and retroperitoneal lymph node adenopathy, splenomegaly with large splenic masses, and heterogenous liver parenchyma, which were all suspicious for underlying lymphoma. The patient underwent liver, bone marrow, and retroperitoneal lymph node biopsies (Figures 1–3) that suggested non-necrotizing granulomatous inflammation in the bone marrow (Figure 1), retroperitoneal lymph node (Figure 3), and necrotizing granulomatous inflammation in the liver (Figure 2). He was diagnosed with sarcoidosis, with initiation of prednisone and methotrexate. He was admitted to the same hospital 3 days prior to his transfer to our hospital with symptoms of chest pain, anorexia, nausea and vomiting, and continued abdominal pain. He was hypotensive on admission with vital signs showing blood pressure 85/63 mmHg, temperature 98.6°F (37°C), pulse 117 beats per minute, respiratory rate 22 breaths per minute, and oxygen saturation 95% on room air. CT thorax was negative for pulmonary embolism but did show moderate right and small-to-moderate left pleural effusions. A CT abdomen and pelvis showed stable changes from prior imaging with new moderate ascites. Urine and blood cultures were negative. His lactate was 2.3 mmol/L (reference range <2.1 mmol/L), INR >12, fibrinogen 50 mg/dL (reference range 180–450 mg/dL), ALT 86 IU/L (reference range <35 IU/L), white blood cell count (WBC) 0.8 K/uL (reference range 3.8–10.6), hemoglobin (Hb) in 7.9 g/dL (reference range 13.5–17), and platelets 92 K/uL (reference range 150–450). He was admitted to the Intensive Care Unit (ICU) with suspected sepsis and started on intravenous fluids, cefepime, and vancomycin, with no clear source of sepsis found. Vitamin K was given for coagulopathy.

Hematology, Infectious Disease, and Rheumatology were consulted. Cefepime and vancomycin were stopped after 5 total days of treatment due to lack of improvement in hematologic and clinical parameters, worsening lactate to 5.3, and no evidence of infection. The etiology of the patient’s pancytopenia was suspected to be intrinsic bone marrow involvement. After discussion with Rheumatology, he was treated with methylprednisolone 1 gram for 3 days, without change in clinical status, and was transferred to our hospital for higher-level care, including bone marrow biopsy. Upon initial evaluation at our hospital, his vital signs were blood pressure 87/64 mmHg, pulse 104 beats per minute, respiratory rate 19 breaths per minute, temperature 98.2°F (36.8°C), and oxygen saturation 99% on room air. Physical examination revealed significant findings of a soft, diffusely tender, mildly distended abdomen with rebound tenderness, positive bowel sounds, and hepatosplenomegaly.

On initial laboratory evaluation, he had pancytopenia with WBC count 0.8 k/uL, Hb 9.3 g/dL, platelets 90 k/uL, absolute neutrophil count (ANC) 0.76 K/uL (reference range 1.80–7.70 k/uL), ALT 146 IU/L, AST 224 IU/L, INR 1.99, prothrombin time (PT) 22 (normal 12.1–14.5 seconds), partial thromboplastin time (PTT) 43 (normal 22–36 seconds), fibrinogen 106 mg/dL (normal 200–450 mg/dL), D-Dimer 5.06 (normal <0.50 micrograms/mL FEU), lactic acid 5.0 mmol/L (normal <2.1 mmol/L),
ferritin 6,420 ng/mL (reference range 24–336 ng/mL), and tri-glycerides 168 mg/dL (reference range 40–200 mg/dL). He was found to have a negative infectious work-up that included blood cultures, urine cultures, tuberculosis cultures, and chest x-ray that was suggestive of small pleural effusions. Cytomegalovirus DNA quantitative was done for pancytopenia and was negative on admission. Parvovirus B19 IgG was positive at 1.39 (index) and IgM was negative, consistent with prior infection. Human immunodeficiency virus 1 and 2 antibody enzyme immunoassay testing was negative 2 months prior to presentation.

He was admitted to the ICU and empirically treated with broad-spectrum antibiotics with vancomycin and cefepime for a presumed clinical picture consistent with sepsis. On hospital day 1, he developed altered mental status. Ammonia level was slightly elevated at 58 umol/L on admission and repeated 5 days and 1 week later, which were both normal. The patient’s glucose levels were slightly elevated at 150 mg/dL and sodium level was 133 mmol/L and ranged from 131 to 140 mmol/L during hospitalization. Due to his altered mental status and lack of clinical and hematological improvement, there was heightened concern for hemophagocytic lymphohistiocytosis. He initially met 3/8 Histiocytosis Society Criteria for HLH including splenomegaly, cytopenia (anemia, thrombocytopenia and neutropenia), and hyperferritinemia. He was started on dexamethasone 20 mg twice daily by mouth for 2 days followed by 20 mg by mouth daily per 10 mg/m² HLH 2004 protocol dosing. A CT head was unremarkable. A bone marrow biopsy was performed the following day that showed hypocellular bone marrow (10–20% cellularity) with trilineage hematopoiesis, no malignancy, no granulomas, and occasional histiocytic hemophagocytosis (Figure 4). His soluble CD 25 (soluble interleukin-2 receptor) level
was elevated at 70 000 pg/mL (reference range <1033 pg/mL), fulfilling 5/8 criteria needed for diagnosis of HLH. Antibiotics were discontinued, and the patient was started on etoposide 150 mg/m² (344 mg) with plan for twice weekly per HLH 2004 protocol. He also received IVIG. Ferritin improved after receiving etoposide. However, the patient’s kidney function worsened. The second dose of etoposide 3 days later was decreased to 75 mg/m² due to worsening kidney (creatinine 1.26 mg/dL to 3.34 mg/dL) function. He was transferred to the floors, where he became hypothermic, developed lactic acidosis of 7.3, and decreased hemoglobin to 5.3. The patient required 2 units of packed red blood cells, 3 units of platelets, and 1 pool of cryoprecipitate for fibrinogen of 89. He became more lethargic and was transferred back to the ICU.

He underwent a repeat work-up for sepsis, with blood cultures negative, and urinalysis negative. A chest x-ray suggested bilateral pleural effusions, underlying airspace disease with worsening edema, and possible multifocal pneumonia. A CT abdomen with oral contrast showed abdominopelvic ascites mildly increased with a new small amount of possible blood products seen dependently in the pelvis. Infectious Disease was consulted and recommended to treat as febrile neutropenia given ANC 690 and WBC 0.6 k/µL. Their recommendation was vancomycin, meropenem, and doxycycline to cover for atypical pulmonary infection, which were all initiated. Fluconazole was also added for possible candidemia due to a catheter-related bloodstream infection as the patient had a Peripherally Inserted Central Catheter Line placed earlier in the hospital course. A fungal workup that was done included whole-blood candida albicans/tropic DNA, candida parapsilosis DNA, and candida krusei/glabrata DNA qualitative PCR magnetic resonance assays, which were all negative. No other fungal workup was recommended by ID. The patient was also started on atovaquone for PCP prophylaxis and valacyclovir. Epstein-Barr Virus (EBV) capsid antibody IgM was negative. EBV capsid antibody IgG was positive and EBV nuclear antibody was positive, consistent with previous infection with EBV. A QuantiFERON Gold was negative, along with 2 specimens of AFB sputum. General Surgery was consulted for possible intraabdominal bleeding that was seen on the CT scan, and they concluded that the patient was a poor surgical candidate secondary to liver failure and thrombocytopenia, with risk of surgery outweighing benefits. Paracentesis and thoracentesis were deferred due to risk of bleeding. General Surgery also recommended a CT angiogram and Interventional Radiology consult for embolization if there is significant drop in hematocrit. Acute pancreatitis was considered in the differential diagnosis, with lipase level of 518 IU/L. The patient was already not receiving anything by mouth and on IV fluids prior to imaging and labs for acute pancreatitis being done. He became oliguric with acute kidney injury. Nephrology was consulted and believed the cause to be multifactorial due to acute tubular necrosis and pre-renal azotemia secondary to multiple contrast exposures, hemodynamic instability, and IV immunoglobulin (IG). A renal ultrasound was negative for obstructive pathology. A third dose of etoposide was held secondary to profound neutropenia (ANC 0), and the patient was started on filgrastim 480 micrograms until his ANC became greater than 1500. Vancomycin was discontinued.

The patient was started on Sustained Low Efficiency Dialysis (SLED) for solute and volume control, as he had greater than 20 liters positive fluid balance with worsening azotemia and confusion. He was also started on bumetanide 0.5 mg/hour. He became obtunded and hypotensive requiring vasopressor support, hypothermic requiring bear hugger, and intubated for inability to protect his airway. Labs showed worsening ALT 1985 IU/L, AST 3322 IU/L, LDH 10,692 IU/L, haptoglobin <30 mg/dL, ferritin 65,620 ng/ml, lactate 14 mmol/L, WBC 0.1 K/µL, hemoglobin 6.5, platelets <10 k/µL, and ANC 0 k/µL.

GI bleed was considered, but the patient was too unstable to have a nuclear bleeding scan or CT angiogram. GI bleed was thought to be the etiology of hypovolemic and hemorrhagic shock. There was also concern for possible intracranial hemorrhage due to thrombocytopenia with platelets below 10 k/µL. An emergent CT head was ordered and showed no evidence of intracranial hemorrhage to explain the patient’s obtunded status. Blood pressure continued to drop, and the patient went into pulseless electrical activity arrest, with unsuccessful resuscitation efforts.

**Discussion**

HLH is an aggressive and often fatal disease associated with a dysregulated immune system response that results in excessive inflammation. HLH can be classified as primary and secondary (acquired). Primary HLH is due to underlying genetic disease and can occur in all age groups, but more commonly in the pediatric population. It is seen in approximately 1 in 50,000 live births [3,4]. Secondary HLH can be due to multiple etiologies, with infectious being the most common, but can include malignancy and autoimmune/rheumatic disease. The most common rheumatic diseases associated with HLH are adult-onset Still’s disease, systemic juvenile idiopathic arthritis, and systemic lupus erythematosus [5]. However, other rheumatic diseases can also be associated with HLH. Sarcoidosis associated with HLH is an extremely rare occurrence. HLH carries a high mortality rate due to the rarity of disease and variable clinical presentation.

The diagnosis of HLH involves a thorough history, physical exam, and laboratory findings. If there is a high clinical suspicion, the workup should include Complete Blood Count (CBC), Basic Metabolic Panel (BMP), Liver Function Testing (LFTs),...
The treatment of HLH involves identifying the precipitating disease and controlling the overactive immune response. Early clinical suspicion is critical in improving outcome. When malignancy or infectious causes are identified, early treatment has been shown to improve outcome. Etoposide works by inhibiting T cells and thereby suppressing cytokine release. Steroids should also be added to further suppress this immune response. If patients are poorly responding to therapy in the first 2–3 days, additional immunosuppressive therapy should be used. It is important to note that, based on expert opinion, it is recommended to treat HLH manifesting with CNS symptoms and hypotension, even if 3 out of 4 modified criteria are met (cytopenias, hepatitis, splenomegaly, and fever). This is recommended because it is common for HLH to present with multiorgan failure (respiratory, CNS, and hypotension) without meeting the full Histiocyte Society guidelines [6].

In adults based on the HLH-94 protocol, the recommended dose of etoposide is 150 mg/m², as induction therapy for 8 weeks however this dose should not be used in macrophage activation syndrome (MAS) [4]. Dosing should be 2 times weekly for the initial 2 weeks and weekly thereafter. For patients with liver disease, dose reduction should be 50% to 75% [4]. Renal failure patients should also have dose adjustment based on their creatinine clearance. Dexamethasone should be given in an IV route in the acute setting, and should then be given by mouth for a total of 8 weeks. Tacrolimus and cyclosporine are immunosuppressants that can be used 8–12 weeks after initial therapy [4]. Tacrolimus has been shown to have less nephrotoxicity and is more commonly used. Patients treated for HLH should also be treated prophylactically for pneumocystis carinii and fungal infections [4]. Patients with MAS should only be treated with dexamethasone and do not require etoposide. If a poor response is seen, treatment of the underlying rheumatic disease should take precedence over guideline-directed HLH therapy [4].

Surveillance is based on response to therapy and clinical improvement in physical exam and laboratory findings; this includes improved splenomegaly, lymphadenopathy, fever, ferritin level, CD 25 IL-2 receptor levels, LFTs, and fibrinogen [4]. Ferritin is an acute-phase reactant and can be used to monitor disease activity; it should be ordered at initial diagnosis and after treatment is started. It is difficult to monitor hemoglobin, WBC, and platelet count with patients on etoposide, as this drug can cause pancytopenia. Our patient was treated with etoposide but developed thrombocytopenia. Our patient was treated with etoposide but developed thrombocytopenia and neutropenia with subsequent discontinuation of the drug after the third dose.

The prognosis of HLH depends on the precipitating cause and underlying etiology. Primary HLH has a poor prognosis and is usually fatal. If left untreated, HLH has a dismal prognosis with a median survival time of only 2 months [4,7]. For secondary HLH in untreated adults, case series have demonstrated a 30-day mortality rate of 20% to 44%, with overall mortality of 50% to 75% [4]. Patients with secondary HLH associated with malignancy have a worse prognosis than those with infectious or rheumatic etiologies. Newer drugs and hematopoietic stem cell transplant have improved survival and even the potential for cure [5].

There have been only 10 case reports of HLH due to sarcoidosis in the literature. Five cases involved concomitant infection in which 4 of those patients died. One patient was successfully treated for disseminated histoplasmosis. Two other cases involved rapidly fatal HLH in patients with a preceding diagnosis of sarcoidosis. Another case reported the successful

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**Table 1. Diagnostic criteria for HLH.**

| A molecular diagnosis compatible with HLH |
|------------------------------------------|
| Five out of the following eight criteria: |
| a. Elevated temperature                   |
| b. Enlarged spleen                        |
| c. Anemia, thrombocytopenia, and neutropenia (need at least 2) |
| d. Elevated fasting triglycerides ≥265 mg/dL and/or fibrinogen level ≤ 1.5 g/L |
| e. Elevated ferritin >500 micrograms/l   |
| g. Biopsy showing hemophagocytosis in the bone marrow, spleen, or lymph nodes |
| h. Low or absent NK cell activity          |
| i. Elevated soluble CD 25 IL-2 receptor ≥ 2400 U/L |

One of the following is needed to meet criteria for HLH (based on the Histiocyte Society guidelines developed in 2004).

Fibrinogen, fasting triglycerides, sCD25, PT, INR, PTT, LDH, and albumin [4]. Diagnosis of HLH is based on guidelines developed by the Histiocyte Society in 2004 [2,4]. Table 1 summarizes the diagnostic criteria needed to confirm HLH. Other clinical findings seen in HLH can be hyponatremia, edema, elevated AST and ALT, abnormal coagulation studies, skin lesions, decreased albumin, increased LDH, increased CRP, increased d-dimer, increased very low-density lipoprotein, decreased high-density lipoprotein, and elevated cerebral spinal fluid protein and cells [4]. Neurological examination can consist of focal deficits and encephalopathy, as seen in our patient. Encephalopathy is also much less common in adults than in children. Bone marrow biopsy is important in the evaluation of HLH, and reveals histiocytosis. These clinical findings are not always seen on initial evaluation, making the diagnosis challenging. Diagnosis of HLH can be difficult due to overlap with other conditions, including hematological and malignant processes. These disease processes can also give rise to HLH, making the diagnosis complex [4].
treatment of HLH and sarcoidosis in a 23-year-old female with IV IG; the patient was also treated with prednisone [7]. The most recent case, reported in 2019, involved a 53-year-old white female with biopsy-proven sarcoidosis involving the liver. She met the criteria for HLH and was successfully treated with pulse-dose steroids [8]. The patient is in 2-year remission and on prednisone 5 mg daily [8]. Five out of these 10 cases resulted in death. In almost every case, the initial presentation mimicked sepsis, but clinical deterioration was evident despite antibiotic use. The spontaneous improvement in sarcoidosis associated with HLH is seen in two-thirds of patients, with the remaining one-third requiring regular follow-up.

Conclusions

The diagnosis of HLH is challenging due to nonspecific clinical and laboratory findings. Early diagnosis and prompt intervention are important in improving outcome. Secondary HLH can have a better response to treatment compared to primary HLH. We are reporting an extremely rare and fatal presentation of HLH associated with sarcoidosis. The lack of response to antibiotics in the setting of clinical and laboratory findings led to the diagnosis of HLH. Even with aggressive treatment similar to previous case reports, the patient clinically deteriorated. HLH must be in the differential diagnosis, even if a diagnosis such as sepsis has been established, and treatment should be instituted early, given the high mortality rate of this condition.

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Conflict of interest

None.

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