A case report of hemophagocytic lymphohistiocytosis (HLH) associated with sarcoidosis

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a rapidly progressing, fatal disorder characterized by severe systemic hyperinflammation presenting with unremitting fever, organomegaly (hepatosplenomegaly), cytopenias, raised inflammatory markers, liver failure, neurological issues, coagulopathy, and multiorgan failure. It is classified as primary due to mutations inherent to the individual causing increased macrophage activation or due to underlying secondary causes ranging from infections, malignancies, metabolic disorders, or rarely, rheumatological disorders such as juvenile idiopathic arthritis, SLE, sarcoidosis, and so on. However, the association between sarcoidosis and HLH has been rarely reported in the literature, which can present with features of sepsis, making the diagnosis challenging and requiring high clinical suspicion. We report the case of a patient with sarcoidosis presenting with recurrent fever, bilateral lower limb swelling, and fatigue, eventually developing fatal HLH that was unresponsive to high-dose steroids.

Keywords: Lymphohistiocytosis, hemophagocytic, sarcoidosis, pancytopenia, hyperinflammation

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal and rare hyperinflammatory syndrome characterized by fever, hepatosplenomegaly, and cytopenias, which can be of genetic etiology or secondary associated with malignancies, autoimmune diseases, or infections. HLH, being a catastrophic cytokine surge, is characterized by a defect in targeted killing and the inhibitory controls of natural killer and cytotoxic T cells, resulting in excessive cytokine production and accumulation of activated T cells and macrophages in various organs where red blood cells, white blood cells, and/or platelets are being attacked by cells in the bone marrow and/or spleen[1]. HLH has pathological immune activation and dysregulated inflammation that cause widespread tissue damage and multi-organ failure. Hypertriglyceridemia, high ferritin level, hypofibrinogenemia, high aminotransferases, and coagulopathy are the most common laboratory findings. Most of the HLH cases are diagnosed and treated on the basis of a protocol released by the Histiocyte Society called HLH-2004 (previously HLH-94)[2,3]. Secondary HLH associated with sarcoidosis is rare and not well reported, requiring early diagnosis for the promotion of early treatment. Sarcoidosis is a chronic systemic granulomatous disease affecting any organs and has different presentations[4].

CASE PRESENTATION

A 58-year-old female with a past medical history of hypertension, tubercular lymphadenopathy (ATT course completed), and sarcoidosis presented with recurrent fever, fatigue, and bilateral lower leg swelling for 10 days. Patient was diagnosed with sarcoidosis three months prior to presentation to our institution on the basis of a trucut biopsy done from the left supraclavicular lymph node showing granulomatous lymphadenitis along with negative tissue GeneXpert, malignancy, and MTB not detected. The patient was started on steroids and showed only mild improvement in symptoms. The fever persisted, followed by right leg swelling and mild dyspnea, which made the patient visit several other hospitals and receive multiple courses of antibiotics.

At the time of admission to our center, the patient was febrile (100.3°F), blood pressure-120/80 mmHg, respiratory rate-19 breaths/min, SpO2- 95%, and heart rate-95 bpm. Physical examination was unremarkable, including normal vesicular breath sounds on auscultation with mild hepatosplenomegaly on palpation. Initial laboratory tests showed pancytopenia with WBC counts-3290 cells/cumm, hemoglobin-5.5 gms%, hematocrit-15.5%, platelet-81,000 cells/cumm, creatinine-1.50 mg/dl, sodium-126 mmol/L, CRP-45.0mg/dl, and a slight rise in total bilirubin level (1.20

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mg/dl). The stool occult blood test done was negative, and the peripheral blood smear (PBS) report revealed normocytic normochromic and microcytic hypochromic RBCs with no atypical cells. DVT screening of bilateral lower limbs was normal with subcutaneous edema only. The CECT chest showed multiple nodular opacities in the bilateral lungs with a few enlarged mediastinal lymph nodes. Extensive infectious workup revealed no source of infection. Cytomegalovirus DNA quantitative done for pancytopenia was negative. A sarcoidosis flare-up was suspected initially, for which an IV steroid (methylprednisolone 125 mg) was started, following which the fever subsided and the patient improved clinically. Pancytopenia and kidney function got better. Hence, the patient was discharged under oral steroid (tapering dose of methylprednisolone 32 mg once a day).

On day 5 of admission, symptoms worsened during the steroid taper with new onset of desaturation (Spo2-92% O2 @ 4 L/min), high-grade fever, and limb swelling. Hence, the patient had an unscheduled visit to the emergency department and was admitted for further management. Laboratory test results were considerably worse, with blood smear microscopy revealing leukocytosis (7660 to 4850 cells/mm^3), thrombocytopenia (76,000 to 40,000 platelets/mm^3), and anemia (hemoglobin, 6.8 to 6.5 g/dL; hematocrit, 19.7 to 18.1%; ferritin-16000 ng/dL; serum LDH, 584 U/L; fibrinogen, 1.53 g/L, D-dimer, 3.65 mg/L and NtproBNP, 1042 pg/mL). The Patient had worsening acute liver failure (total bilirubin-13.20 mg/dl, conjugated bilirubin-7.30, ALT/AST-84/126) and acute kidney injury (creatinine-2.30, urea-211, sodium-11, potassium-5.60). Pulse steroid therapy (methylprednisolone 500 mg) and intravenous meropenem and aztreonam were started. Blood transfusion and hyponatremia correction done with 3% NaCl. Chest x-ray showed right middle zone collapse consolidation. A Rheumatology consultation was done, and it was advised to repeat the ANA (IFA) and ENA profiles, which came back negative. Bone marrow aspiration and biopsy were done, which were consistent with abundant intracellular, encapsulated, ovoid yeast forms in neutrophils with increased hemophagocytosis. According to the HLH-2004 protocol, a diagnosis of hemophagocytic lymphohistiocytosis (HLH) was established as she initially met ⅜ Histiocytosis Society Criteria for HLH, including splenomegaly, cytopenia (anemia, thrombocytopenia, and neutropenia), and hyperferritinemia. The patient was started on methylprednisolone pulse therapy (500 mg) and planned for etoposide if tolerated and improved with steroids. Later during the hospital stay, the case got complicated by worsening anemia, thrombocytopenia, progressive liver failure, renal failure, and urine infection with culture showing Pseudomonas aeruginosa manifested with bilateral pleural effusion, increased oxygen demand, abdominal pain, and hematochezia suggestive of DIC, urosepsis, and uremic/hepatic encephalopathy with multiorgan dysfunction syndrome requiring ICU admission. The worsening laboratory reports are listed in table 1. Hence, the patient was shifted to the ICU, and higher-generation antibiotics, antifungals, and supportive measures were modified as per ICU protocol. The worsening chest x-rays of the patient are illustrated in figure 1. Nephrology and gastroenterology consultations were done for ongoing renal failure and sudden upper GI bleeding. However, the patient was very critical of undergoing any interventions. Her respiratory status deteriorated (15L O2 via NRBM) with a drop in GCS to 7/15 and multiple episodes of active PR bleeding leading to a drop in platelet counts to 30,000/mm^3, Cr-3, Ur-304, and total bilirubin-16.70. The patient didn't qualify for a trial of intravenous immunoglobulin (IVIG) and didn't respond to pulse steroid therapy as well. The patient's family signed for DNI/DNR status and decided on a transition to comfort care. She unfortunately expired due to neutropenic sepsis with multiorgan failure before we could escalate the treatment for sarcoidosis-driven HLH.

Table 1: Worsening Laboratory Values

INVESTIGATIONS	First Admission	Second Admission	ICU
Total leucocytes counts (TLC)	3290 cells cumm	7660 cells cumm	4850 cells cumm
Hemoglobin (HB)	5.5 gms%	6.6 gms%	6.5 gms%
Packed cell volume (PCV)	15.5%	19.7%	18.1%
Platelets	81000 cells cumm	76000 cells cumm	40000 cells cumm
Creatinine (Cr)	1.50 mg/dl	2.90 mg/dl	3 mg/dl
Urea (Ur)	57.50 mg/dl	211 mg/dl	304 mg/dl
Sodium (Na)	126 mmol/l	125 mmol/l	136 mmol/l
Potassium (K)	4.70 mmol/l	4.3 mmol/l	4.8 mmol/l
Total protein	5.40 g/dl	2.3 g/dl	4.3 g/dl
Albumin	2.50 g/dl	2.2 g/dl	2.3 g/dl
Alanine Transaminase (ALT)	38 U/L	84 U/L	130 U/L
Aspartate Transaminase (AST)	43 U/L	126 U/L	138 U/L
Alkaline Phosphatase (ALP)	170 U/L	322 U/L	302 U/l
Total Bilirubin	1.20 mg/dl	13.2 mg/dl	16.60 mg/dl
Unconjugated Bilirubin	1.0 mg/dl	1.3 mg/dl	10.0 mg/dl
Conjugated Bilirubin	0.20 mg/dl	7.30 mg/dl	11.10 mg/dl

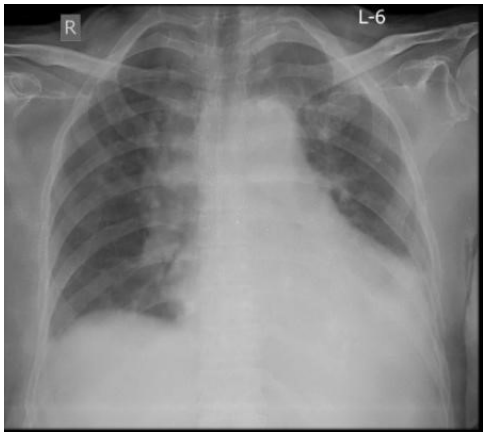

Figure 1a- 1st admission

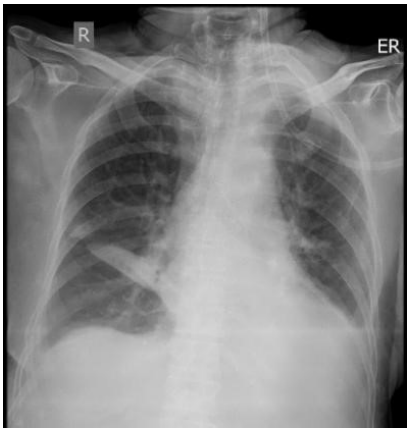

Figure 1b- 2nd admission

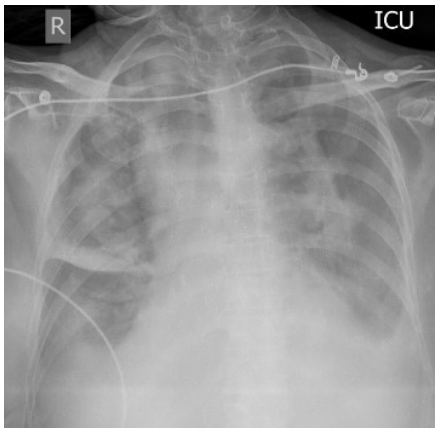

Figure 1c- ICU stay

Figure 1: Chest X-rays showing progressive increase in bilateral lung nodular opacities, collapse consolidation, and pleural effusion.

DISCUSSION

Sarcoidosis is a chronic granulomatous disease associated with an inappropriate T cell-mediated immune response predominantly affecting young African American females. HLH is an aggressive and often fatal disease occurring as a result of rapidly fatal proliferation of histiocytes with subsequent hemophagocytosis, which results in excessive inflammation due to dysregulated immune system response that causes widespread tissue damage and multi-organ failure[1]. Secondary HLH is less age-restricted, and although it can occur in young children, it is more common in older children and adults who present with no known genetic cause or family history of HLH. It can be due to various etiologies, with infectious being the most common cause (Epstein-Barr virus, herpes simplex virus, cytomegalovirus, avian influenza), but can include malignancy and autoimmune/rheumatic disease. Sarcoidosis associated with HLH is an extremely rare occurrence that carries a high mortality rate and variable clinical presentation, making early diagnosis difficult[1,2].

The diagnosis of hemophagocytic lymphohistiocytosis (HLH) requires five of eight criteria, including persistent fever, an enlarged spleen (hepatosplenomegaly), cytopenias (anemia, thrombocytopenia, neutropenia), elevated ferritin levels (>500 mcg/L), high triglyceride levels (>265 mg/dL), or low fibrinogen levels (below 1.5 g/L), hemophagocytosis on biopsy, low/absent natural killer (NK) cell activity, and elevated soluble CD25 (interleukin-2 receptor) above 2400 U/L. Meeting a combination of these criteria is necessary for confirming HLH. Five of these eight criteria must be fulfilled unless the family history of genetic diagnosis is consistent with HLH[2]. Usually, there is no single feature which is specific for HLH, including hemophagocytosis, but the triad of prolonged fever, hepatosplenomegaly, and cytopenias, like in our case, should arouse suspicion of the possibility of HLH. Whenever HLH overlaps with other medical conditions, including hematological and malignant processes, no clinical features appear on initial evaluation, making diagnosis challenging[3,4].

Most likely, the mechanisms underlying secondary forms of HLH are multifactorial. Studies suggested that dysregulation of inflammatory and immune systems can cause peripheral T-cell expansion and reduce NK cell activity, which contributes to the condition causing increased cytokine release from T-cells and macrophages, such as interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-α), interferon gamma (IFN-γ), and soluble IL-2 receptor (sIL-2R). Upon this inflammatory response, proliferation and activation of antigen-presenting cells, including macrophages, histiocytes, and CD8+ T cells, promote the phagocytosis of other cells[4]. As has been shown in patients with sepsis, the expression of both pro- and anti-inflammatory cytokines may lead to the apoptosis of cells of the innate and adaptive immune systems[4,5]. The initial presentation is often vague, typically involving symptoms such as fever and swollen lymph nodes. Around 50% of affected individuals may arrive in the ICU showing signs that resemble sepsis, along with varying degrees of organ dysfunction. Besides, patients may present with respiratory symptoms like cough, dyspnea, or respiratory failure, especially where the trigger is a respiratory infection. Around 25% of cases may present with neurological symptoms like seizures, meningitis, or cerebral hemorrhage. On average, it takes about 3.5 months from the onset of symptoms to reach a diagnosis of HLH, and the activated inflammatory cytokines often persist for 100 days[5,6,7]. In the study done by Fukaya et al.[9], fever was present in 87% of the patients, followed by leukopenia and thrombocytopenia in 87%, elevated D-dimer levels in 96%, and neuropsychiatric symptoms in 30% of the patients.

In fact, cases of HLH secondary to sarcoidosis are very rare. Dhote et al.[6] studied 26 patients with secondary HLH, one of whom had pulmonary sarcoidosis, and Lam KY et al.[7] reported a case of sarcoidosis with miliary tuberculosis

complicated by HLH. Patients had clinical findings of fever, thrombocytopenia, and elevated triglycerides in both of these cases, similar to our study, where patients didn't survive due to late diagnosis and treatment failure. In a similar study conducted by Bártholo et al.[8], a patient with a history of long-standing sarcoidosis presented with episodes of fever and fatigue. Hemophagocytic syndrome was diagnosed through bone marrow aspiration. However, due to inadequate treatment, the patient progressed to a sepsis-like condition that ultimately resulted in multiorgan failure. In our case as well, patients had nonresolving intermittent fever, fatigue, and pancytopenia, which later developed into sepsis, leading to multiorgan dysfunction and mortality. Bone marrow aspiration and biopsy should be performed in patients with thrombocytopenia or leukopenia of unknown cause, as was the case in our patient. Fukaya et al.[9] evaluated 1014 patients with systemic autoimmune diseases. where 30 cases of HLH associated with SLE were identified with 3% prevalence, and none of the cases in this study were related to sarcoidosis. Similarly, only 5 cases of HLH were associated with sarcoidosis, where SLE was the most common in a study done by Atteritano et al[10]. Phillips et al.[11] reported a case of a 69-year-old male with sarcoidosis associated with HLH treated with corticosteroids, etoposide, and cyclosporine, and the Patient was cured under regular follow-up. Another case reported by Balduini et al.[12] 23/female treated with intravenous gamma globulin and prednisone also recovered. Lam et al.[13] reported a case of a 42-year-old male who died before receiving treatment, and Okabe et al.[14] reported 2 cases of a 32-year-old male treated with methylprednisolone and intravenous immunoglobulin (IVIG) and a 68-year-old female treated with infliximab and cyclosporine who didn't survive as well. So limited number of cases of HLH associated with sarcoidosis are reported in the English literature so far, and most of them had poor outcomes.

Treatment for hemophagocytic lymphohistiocytosis should be started if the disorder is suspected, even if not all diagnostic criteria are fulfilled. The goal of therapy in adult patients with HLH is to suppress the immune system and quiet the unregulated severe hyperinflammation. The treatment of HLH involves identifying the precipitating cause and controlling the overactive immune response. Early clinical suspicion is critical in improving outcomes. When malignancy or infectious causes are identified, early treatment has been shown to improve outcome[10,11]. The HLH-94 protocol integrates cytotoxic and immunomodulatory treatments, starting with an 8-week remission-induction phase using etoposide (VP-16) and high-dose dexamethasone.

For patients whose central nervous system (CNS) HLH does not improve after two weeks of dexamethasone, intrathecal methotrexate (IT MTX) may also be included. This induction phase is followed by systemic continuation therapy with cyclosporine A[1,12]. A more recent modification in 2004 (HLH-2004 protocol) intensifies treatment with cyclosporine A at the beginning of induction and adds hydrocortisone to intrathecal methotrexate with the hope of preventing reactivation of HLH. Corticosteroids may be used as monotherapy for secondary causes of HLH; however, treatment should be broadened if the disorder progresses[2]. If left untreated, the prognosis of HLH is poor and generally fatal. Therefore, prompt recognition and timely treatment are crucial.

Mortality in secondary HLH has been reported to vary from 8–22% in rheumatologic HLH to 18–24% in EBV HLH. Delay in the diagnosis of multiorgan involvement is associated with a poorer prognosis in both primary and secondary HLH patients, and prompt treatment must be instituted to prevent end-organ irreversible damage. Unfortunately, many of these patients will succumb to bacterial and/or fungal infections from prolonged neutropenia, multi-organ damage, or cerebral dysfunction[6,7].

CONCLUSION

In conclusion, secondary HLH associated with sarcoidosis is extremely rare, and our case highlights the timely diagnosis to start therapy to decrease associated morbidity and mortality. Frequently, diagnostic criteria are not yet fulfilled at initial presentation due to non-specific clinical and laboratory findings, which often delay the diagnosis of HLH, affect patient outcomes. In our case, the patient clinically deteriorated despite aggressive treatment, like previous case reports, which imparts us with the lesson of keeping HLH in the differential diagnosis whenever any patient with rheumatic/autoimmune diseases presents with prolonged fever, hepatosplenomegaly, and cytopenias or a diagnosis of sepsis has been established, given the high mortality rate of this condition. The future goals should include modification of the current treatment protocol and enrollment of HLH patients in any clinical trials. Goals for the future include biomarker identification, genetic profiling, understanding the mechanism of HLH, and modification of the current treatment protocol. Whenever possible, patients with HLH should be enrolled in clinical trials.

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INFORMED CONSENT STATEMENT

The informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

The data of this study are available from the corresponding author upon reasonable request.

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None

CONFLICT OF STATEMENT

None

REFERENCES

1. Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. Expert Rev Clin Immunol. 2010;6(1):137-54.
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. Pediatric blood & cancer. 2007 Feb;48(2):124-31.
3. Atteritano M, David A, Bagnato G, Beninati C, Frisina A, Iaria C, Cascio A. Haemophagocytic syndrome in rheumatic patients. A systematic review. European Review for Medical & Pharmacological Sciences. 2012 Oct 1;16(10).
4. Bártholo TP, Pugliese JG, Mafort TT, Silva VL, Costa CH, Rufino R. Hemophagocytic syndrome due to pulmonary sarcoidosis. Jornal Brasileiro de Pneumologia. 2012;38:666-71.
5. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. Nature Reviews Immunology. 2006 Nov 1;6(11):813-22.
6. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, Dupond JL, Larroche C, Piette AM, Mechenstock D, Ziza JM. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2003 Oct 15;49(5):633-9.
7. Lam KY, Ng WF, Chan AC. Miliary tuberculosis with splenic rupture: a fatal case with hemophagocytic syndrome and possible association with long standing sarcoidosis. Pathology. 1994 Jan 1;26(4):493-6.
8. Bártholo TP, Pugliese JG, Mafort TT, Silva VL, Costa CH, Rufino R. Hemophagocytic syndrome due to pulmonary sarcoidosis. Jornal Brasileiro de Pneumologia. 2012;38:666-71.
9. Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, Atsumi T, Koike T. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. Rheumatology. 2008 Nov 1;47(11):1686-91.
10. Atteritano M, David A, Bagnato G, Beninati C, Frisina A, Iaria C, Cascio A. Haemophagocytic syndrome in rheumatic patients. A systematic review. European Review for Medical & Pharmacological Sciences. 2012 Oct 1;16(10).
11. Phillips J, Staszewski H, Garrison M. Successful treatment of secondary hemophagocytic lymphohistiocytosis in a patient with disseminated histoplasmosis. Hematology. 2008 Oct 1;13(5):282-5.
12. Balduini CL. Hemophagocytic syndrome responding to high-dose gammaglobulin as presenting feature of sarcoidosis. Am J Hematol. 1997;54:88-9.
13. Lam KY, Ng WF, Chan AC. Miliary tuberculosis with splenic rupture: a fatal case with hemophagocytic syndrome and possible association with long standing sarcoidosis. Pathology. 1994 Jan 1;26(4):493-6.
14. Okabe T, Shah G, Mendoza V, Hirani A, Baram M, Marik P. What intensivists need to know about hemophagocytic syndrome: an underrecognized cause of death in adult intensive care units. Journal of intensive care medicine. 2012 Feb;27(1):58-64.