Frontiers in Medical Case Reports, ISSN: 2582-8142

Hemophagocytic Lymphohistiocytosis Associated with Sarcoidosis: A Case Report and Review of the Literature

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Received: 16 July 2020; **Accepted:** 12 August 2020

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal inflammatory syndrome characterized by histiocyte proliferation and hemophagocytosis. Primary HLH primarily occurs in children and is caused by genetic mutations. Secondary HLH, more often seen in adults, occurs as a result of infections, malignancies or rarely rheumatic diseases. HLH secondary to sarcoidosis is rare. We present a case of HLH associated with recently diagnosed sarcoidosis in a 61-year-old female.

Keywords: *Hemophagocytic Lymphohistiocytosis, Sarcoidosis, Histiocyte Proliferation*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal inflammatory syndrome characterized by histiocyte proliferation and hemophagocytosis (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). It often presents with fever, hepatosplenomegaly and pancytopenia (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003; Henter *et al*., 2007). HLH is classified as primary or secondary (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008). Primary HLH, which is more common in the pediatric population is caused by genetic defects of immune system regulation while secondary HLH is often triggered by infections, malignancies or rheumatic diseases in susceptible individuals (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). Diagnosis of most HLH cases follow the Histiocyte Society guidelines (Table 1) (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Henter *et al*., 2007). The diagnosis of secondary HLH is made on clinical and pathologic findings. Five of eight criteria are considered necessary for the diagnosis of secondary HLH (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Dhote *et al*., 2003; Henter *et al*., 2007). If left untreated, patients with HLH will likely progress to multi organ failure and death. Even with treatment, there is a

high mortality rate with this disease (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Dhote *et al*., 2003; Henter *et al*., 2007).

HLH secondary to rheumatic disease is rare (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). It is often associated with systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis and Still's disease (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). It is rarely associated with sarcoidosis (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). Sarcoidosis is an idiopathic granulomatous disease that can affect any organ, but often involves the lung (James *et al*., 2018). The pathogenesis of sarcoidosis is unknown, but it is believed to be driven by antigens (James *et al*., 2018).

Case Presentation

A 61-year-old female with a past medical history of hypertension, diabetes and neuro sarcoidosis (treated with a 2-week course of steroids) was transferred to our institution for pancytopenia, neutropenic fever and bilateral lower extremity weakness. She presented to an outside hospital with a month history of bilateral lower extremity weakness and falls. MRI brain, cervical, thoracic and lumbar spine did not reveal acute spinal abnormalities. During her hospital stay, her pancytopenia worsened, and she also developed fevers. Infectious work up at the outside hospital was negative.

On arrival at our institution, vitals were within normal limits. Her physical exam was notable for dysconjugate gaze, decreased motor strength in the left hand, diminished reflexes in left lower extremity, decreased left hip flexion, decreased dorsiflexion of the left foot and decreased plantar flexion of her left leg.

Complete blood count revealed leukopenia (0.97 K/uL, Absolute neutrophil count 710 K/uL), anemia (8.8 g/dL) and thrombocytopenia (81 K/uL). The comprehensive metabolic panel revealed elevated alkaline phosphatase (855 U/L), aspartate aminotransferase (AST) (369 U/L), alanine aminotransferase (ALT) (244 U/L) and serum creatinine (1.30 mg/dL). Report of bone marrow at outside hospital revealed numerous non-caseating granulomas involving an otherwise mildly hypercellular marrow with trilineage hematopoiesis consistent with sarcoidosis.

The patient was evaluated by neurology, hematology, rheumatology, infectious disease and nephrology teams. Magnetic resonance imaging (MRI) of brain, cervical, thoracic and lumbar spine were repeated at our institution and revealed enhancement of multiple nerve roots without associated enlargement or associated mass lesion. Lumbar puncture was unrevealing. Infectious work up included negative blood cultures, EBV IgM, HIV, CMV and hepatitis serologies. See Table 2 for infectious work up.

Table 1: Diagnostic criteria of HLH-2004

Diagnostic criteria of HLH-2004
A. Molecular diagnosis consistent with HLH (i.e., identification of an HLH-associated gene mutation, such as PRF1, UNC13D, STX11, and others) or B. Meets 5 of the 8 Criteria • Fever • Splenomegaly • Cytopenia (affecting > or equal 2 lineages in the peripheral blood): Hemoglobin <9 gm/dl, platelets <100x10^9/L and neutrophils <1x10^9/L • Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides greater than or equal to 265 mg/dl, fibrinogen less than or equal to 1.5 gm/L • Hemophagocytosis in bone marrow or spleen or lymph nodes (no evidence of malignancy) • Ferritin greater than or equal to 500 ug/l • Soluble IL-2 receptor greater than or equal to 2400 U/ml (sCD25) • Low or absent NK-cell activity

Table 2: Infectious Work Up

Plasma/Blood Studies	
HIV 1,2 Combo (Ag/Ab)	Non reactive
Hepatitis Panel (Hep B Core Ab, Total, Hep C Antibody IA, HBsAg, Hep B Surface Ab, Qual)	Negative
Epstein-Barr VCA IgG	Positive
Epstein-Barr VCA IgM	Negative
EBV DNA	Not Detected
CMV IgG Antibody	Positive
CMV IgM Antibody	Negative
CMV DNA Detection and Quant	Not Detected
Parvovirus B19 PCR	Not Detected
Herpes Virus 6 IgG Antibody	1:160
HHV6 Human Abs, IgM	Not Detected
Cryptococcus Ag Detection	Negative
Lyme Abs, IgG/IgM, late >30 days symptoms	Positive
Lyme IgG Western Blot	Negative
Toxoplasma PCR	Not Detected
Syphilis IgG with confirmation	Non Reactive
Blood Parasites	Negative
Blood TB Screen	Indeterminate
AFB Culture	No acid fast bacilli isolated
3 sets of blood cultures during admission	Negative
Blood cultures on last day (resulted after death)	Positive for Vancomycin Resistant Enterococcus (VRE)
Fungal Histoplasma Blood Culture	No fungus isolated
CSF Lab Tests	
CSF Culture and Stain	No growth
EBV Quant	Negative
CSF Fluid	Negative for malignant cells
Fungal CSF Cult/CAD	No fungus isolated
BAL/lung Biopsy Studies	
Tissue culture and stain	No growth
Legionella culture only	No Legionella species
Nocardia culture and stain	No growth
Fungal culture and smear	No fungus

HSV PCR	Not Detected
AFB culture and stain	No acid fast bacilli
CMV culture	Negative
Pneumocystis Jiroveci PCR	Negative
Aspergillus Galactomannan	Negative
AFB culture and stain	No acid fast bacilli isolated
Fungal culture and smear	No fungus isolated
Anaerobe culture	Negative for anaerobes
Bone Marrow Studies	
Body fluid culture and gram stain	No growth
AFB culture	No acid fast bacilli
Urine Studies	
Histoplasma Urine Antigen	None Detected
Legionella PCR	Negative

Further work up revealed ferritin and triglycerides were elevated at 3,000 ng/mL and 279 mg/dL respectively. Fibrinogen was noted to be low at 103 mg/dL. Computed tomography (CT) of abdomen and pelvis revealed hepatosplenomegaly and upper abdominal lymphadenopathy.

There was concern for HLH due to patient meeting five of the eight criteria including fever, pancytopenia, splenomegaly, hypertriglyceridemia and elevated ferritin. High dose dexamethasone was started on hospital day 4 while awaiting further testing. Bone marrow biopsy was repeated at our institution on day 7 of admission and did not reveal noncaseating granulomas but revealed evidence of hemophagocytosis (Fig. 1).

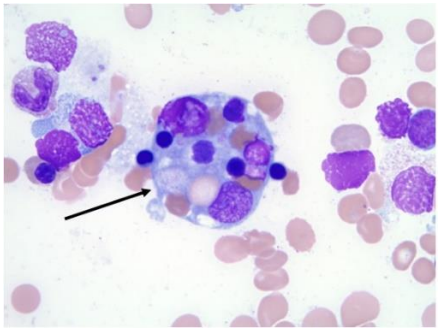

Figure 1: Bone Marrow Aspirate (Wright Giemsa stain) demonstrating hemophagocytosis
Black arrow points to a hemophagocyte which has ingested nuclear red blood cells, mature red blood cells and granulocytic precursors

Outside hospital bone marrow biopsy slides were reviewed by our hematology pathologists and did not show noncaseating granulomas but instead showed histiocytes with some in clusters.

Patient continued to deteriorate with persistent fevers and soluble interleukin receptor resulted as 3577 u/mL. Due to concern of incorrect diagnosis of sarcoidosis, further work up was performed to find driving factor of HLH. To evaluate for possible lymphoma as the driver of HLH, a positron emission tomography (PET) scan was done (Fig. 2).

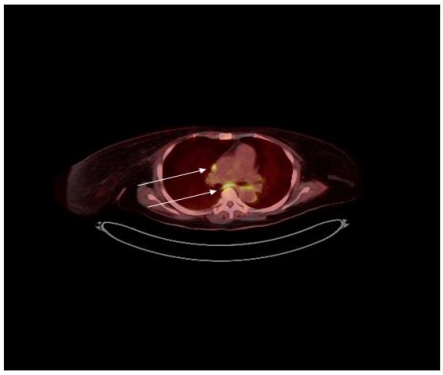

Figure 2: PET Scan: Multiple borderline/mildly enlarged hypermetabolic mediastinal and hilar lymph nodes. White arrows point to mildly hypermetabolic lymph nodes

PET scan revealed several hypermetabolic mediastinal and hilar lymph nodes and several nonspecific mild hypermetabolic lymph nodes in the upper abdomen (SUV 5.6-9.9, consistent with reactive lymphadenopathy instead of neoplasm). Biopsy of liver and mediastinal lymph nodes were obtained. The mediastinal lymph node biopsy showed evidence of sarcoidosis (granulomatous lymphadenitis) and no evidence of malignancy or infection (Fig. 3 and 4).

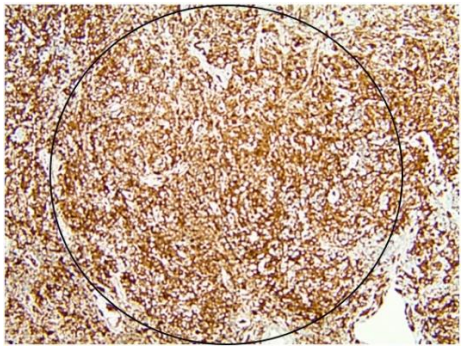

Figure 3: Lymph node biopsy (CD163 stain) demonstrating collections of macrophage forming a loose granuloma (circled)

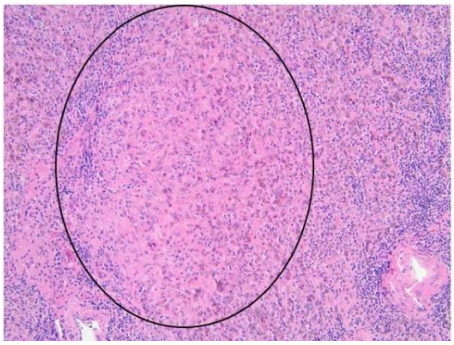

Figure 4: Lymph node biopsy (HE stain) demonstrating collections of macrophage forming a loose granuloma (circled)

The consensus from multiple specialty teams was to treat as sarcoidosis driven HLH. Patient was transferred to malignant hematology service to escalate therapy to include etoposide. However, on evening of transfer, she was found unresponsive with hypotension and hypoglycemia. She was intubated and transferred to the medical intensive care unit and treated for sepsis. She remained hypotensive despite four vasopressors and died on hospital day 34.

Our patient presented to us with pancytopenia, neutropenic fever and bilateral lower extremity weakness. HLH was suspected and an extensive work up to determine the triggering factor was undertaken. She remained neutropenic for most of her stay and unfortunately expired due to neutropenic sepsis before initiation of escalated treatment for sarcoidosis driven HLH.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal inflammatory syndrome characterized by histiocyte proliferation and hemophagocytosis (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). It often presents with fever, hepatosplenomegaly and pancytopenia (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). It was first described in 1939 and can be classified as primary or secondary (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008). Primary HLH is due to genetic mutations in PRF 1, UNC13D, STX11 genes and others and is usually diagnosed in the first two years of life (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008). It has an incidence of 1/50,000 and is inherited in an autosomal recessive pattern (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012). There are five known types of primary HLH known as familial hemophagocytic lymphohistiocytosis (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Fukaya *et al*., 2008). Primary HLH can also be associated with other primary immunodeficiency syndromes such as Chediak-Higashi syndrome, X-linked lymphoproliferative syndromes and Griscelli syndrome (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Fukaya *et al*., 2008).

Secondary HLH occurs during adulthood in most patients (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). It is usually associated with infections, malignancies and rarely rheumatic diseases (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). Other causes include medications such as chemotherapeutic agents (Bartholo *et al*., 2012).

HLH occurs due to the proliferation of histiocytes in the bone marrow and reticuloendothelial system (Dhote *et al*., 2003). This is induced by a cytokine storm that affects the function of T lymphocytes and natural killer cells and leads to prolonged and excessive activation of antigen presenting cells (Bartholo *et al*., 2012). The Histiocyte Society developed the diagnostic criteria for HLH

in 1994 which included fever, splenomegaly, bicytopenia, fasting hypertriglyceridemia and/or hypofibrinogenemia and hemophagocytosis (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Henter *et al*., 2007).

HLH-1994 was updated in 2004 to include elevated ferritin, high soluble Interleukin receptor-2 receptor levels and low or absent NK-cell activity (Table 1) (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Henter *et al*., 2007). Five of these eight criteria must be fulfilled unless family history of genetic diagnosis is consistent with HLH. HLH-2004 treatment protocol recommends chemo-immunotherapy etoposide, dexamethasone and cyclosporine (Henter *et al*., 2007). However, this protocol was designed for patients under 18 years old which poses a dilemma for adults who present with HLH (Henter *et al*., 2007). Dexamethasone and etoposide are often used as first line treatment in adults with HLH (Abughanimeh *et al*., 2018; Henter *et al*., 2007). In most patients, treating the underlying disorder such as infection is key to controlling HLH (Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003).

Abughanimeh *et al*. reported a similar case of a recently diagnosed sarcoidosis patient who developed HLH and did not respond to high dose steroids or IVIG. He documented 8 cases in addition to their case where sarcoidosis was implicated in HLH. Four of the cases reported were triggered by miliary tuberculosis, disseminated histoplasmosis and EBV in patients with sarcoidosis (Abughanimeh *et al*., 2018).

HLH driven by rheumatic disease is rare (Abughanimeh *et al*., 2018; Bartholo *et al*., 2012; Atteritano *et al*., 2012; Fukaya *et al*., 2008; Dhote *et al*., 2003). Fukaya *et al*. reviewed patients with systemic autoimmune disease admitted to their institution over a ten-year period. Of the 1014 patients recruited, only 30 cases of HLH were identified. Patients with SLE were more likely to have HLH in this study and no cases of sarcoidosis were reported (Fukaya *et al*., 2008). Atteritano, *et al*. in a systemic review of the literature identified 421 patients with autoimmune disease who had documented HLH. Most patients had systemic juvenile arthritis, SLE and Still's disease with only five patients having sarcoidosis (Atteritano *et al*., 2012). Dhorte *et al*. also studied the association of HLH and systemic disease in France over a 2 year period. There were 26 cases identified with most patients having SLE and one patient who had sarcoidosis (Dhote *et al*., 2003).

Conclusion

In conclusion, HLH triggered by sarcoidosis is rare but is reported in the literature. Our case highlights the challenges in identifying the underlying trigger for HLH and the need for timely and accurate diagnostic evaluations. Sarcoidosis driven HLH should be entertained in patients who present with features of HLH and have a diagnosis of sarcoidosis. Expedited work up and treatment should be sought to decrease the mortality associated with this aggressive and often fatal disease.

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