



Case report

Hemophagocytic lymphohistiocytosis secondary to disseminated histoplasmosis, cytomegalovirus viremia, and nontuberculous mycobacteria bacteremia in a patient with recently diagnosed AIDS

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ABSTRACT

A 30-year-old Honduran male with recently diagnosed AIDS presented with a 1-month history of worsening abdominal pain, diarrhea, and fever. Initial investigations were notable for Cytomegalovirus viremia and diffuse lymphadenopathy. Axillary lymph node biopsy demonstrated necrotizing lymphadenitis with disseminated histoplasmosis. Despite aggressive antimicrobial therapy he continued to clinically deteriorate raising suspicion for hemophagocytic lymphohistiocytosis. The patient met 5 of 8 HLH-2004 diagnostic criteria and was successfully treated with dexamethasone and etoposide per the HLH-94 protocol. Despite the high mortality rates and poor clinical outcomes of hemophagocytic lymphohistiocytosis in patients living with HIV/AIDS, this case demonstrates that this high-risk patient population can be successfully treated and survive acquired hemophagocytic lymphohistiocytosis. Furthermore, our case stresses the importance of maintaining a broad differential diagnosis in patients living with HIV/AIDS who present with sepsis.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening systemic clinical syndrome resulting from excessive, yet ineffective, immune system activation. HLH is primarily observed in infants and children, however, it can occur in adults of all ages. HLH may be inherited or acquired. Infections, malignancies, rheumatologic disorders, and immunodeficiency syndromes may all trigger HLH [1,2]. In patients living with AIDS, HLH is most commonly secondary to infectious etiologies. Intracellular organisms such as Epstein Barr virus (EBV), Cytomegalovirus (CMV), mycobacteria, and fungi are common inducers of HLH [1,3,4]. Many of these HLH triggering intracellular organisms are also common opportunistic infections observed in patients living with HIV/AIDS or malignancies. HLH has been shown to have significant mortality in HIV/AIDS even in the setting of appropriate therapy. The mortality of HLH in patients living with HIV/AIDS has been documented to be greater than 40%. We report a unique case of HLH secondary to disseminated histoplasmosis, CMV viremia, and nontuberculous mycobacteria (NTM) bacteremia in a young male with recently diagnosed AIDS that was successfully treated. This case also stresses the importance of understanding the geographic distribution of

typical opportunistic organisms.

Case presentation

Patient information

A 30-year-old Honduran male with recently diagnosed AIDS presented to the emergency department with a 1-month history of worsening abdominal pain, diarrhea, weight loss, fever, and chills. Diagnosis of AIDS, *Campylobacter* and enteropathogenic *Escherichia coli* colitis/duodenitis had been made 3 weeks earlier. He had a decreased CD4 count of 19/uL (reference range 359–1519) and an elevated HIV-1 viral load of 2.19 million copies/mL. He completed a 2-week course of antibiotics (levofloxacin and metronidazole). Two days prior to arrival, he began bicitegravir, emtricitabine, and tenofovir alafenamide for HIV. His past medical history included malaria as a young child. He denied any surgical history.

He immigrated to the Southwest United States from Honduras approximately 5 years earlier, and more recently moved the Southeast United States. His social history was also notable for unprotected sex with both male and female partners. On exam he was febrile with a

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temperature of 101 °F, tachycardic at 120 beats per minute with a blood pressure of 97/55 mmHg. He appeared diaphoretic and cachectic. Diffuse abdominal tenderness was noted without guarding or rebound tenderness. Skin and lymphatic exams were unremarkable on initial presentation, but he later developed rash as well as diffuse lymphadenopathy.

Investigations

Initial laboratory work was notable for transaminitis (total alkaline phosphatase 400 IU/L, SGOT/AST 480 U/L and SGPT/ALT 183 U/L; reference ranges 53–148, ≤ 55, 5–34, respectively) and microcytic anemia (hemoglobin 7.7 g/dL, hematocrit 23.8 %, and a mean corpuscular volume (MCV) of 78 fL; reference ranges 12.6–17.7, 37.5–51, 79–97, respectively). Computed tomography (CT) imaging revealed pancreatitis and duodenitis, extensive mesenteric and aortocaval lymphadenopathy with mesenteric edema, numerous bilateral pulmonary nodules, and bilateral axillary adenopathy. Right upper quadrant ultrasound demonstrated hepatomegaly.

An extensive infectious disease work-up was performed (Table 1). Initial results were notable for a positive CMV quantitative PCR (642 IU/mL). Later in his hospitalization, we noted a positive *Histoplasma* blood and urine antigen. BAL cultures ultimately grew *Histoplasma capsulatum*. Pulmonary nodule biopsy was negative for malignancy but positive for fungal organisms. Additionally, an axillary lymph node biopsy demonstrated necrotizing lymphadenitis (Fig. 1 and Fig. 2). Bone marrow biopsy was also consistent with *Histoplasma capsulatum* (Fig. 3 and Fig. 4). Around the time biopsies were obtained, the patient developed skin lesions on the face consistent with disseminated histoplasmosis (Fig. 5).

Despite continued broad coverage with meropenem, ganciclovir, and amphotericin B liposomal, the patient continued to have fevers and developed pancytopenia. This was concerning for the development of immune reconstitution inflammatory syndrome (IRIS) versus HLH. Ferritin levels were significantly elevated at 83,075 ng/mL (reference range 28–365). Intravenous steroids were initiated, and hematology was consulted. IL-2 receptor alpha level was elevated at 5265 U/mL (reference range 223–710). The patient was diagnosed with HLH based on the HLH-2004 diagnostic criteria (Table 2) [5]. His qualifying factors included elevated ferritin, elevated IL-2 receptor alpha, fever, splenomegaly, and pancytopenia in the setting of HIV, histoplasmosis, and CMV infections.

Treatment

The patient’s numerous antimicrobial medications were frequently adjusted over his prolonged hospitalization. Ganciclovir was started early in his hospitalization for empiric viral coverage and was continued when the diagnosis of CMV viremia was confirmed. He was placed on itraconazole 300 mg twice daily early in his hospitalization for *Blastomyces*, *Histoplasma*, and *Coccidioides* empiric coverage. However, with pathologic findings of disseminated histoplasmosis on axillary lymph node and bone marrow biopsies, itraconazole was changed to amphotericin B liposomal 5 mg/kg/dose IV daily. After completing 14 days of amphotericin B liposomal, the patient was transitioned back to itraconazole to complete a 12-month course. Bictegravir, emtricitabine, and tenofovir alafenamide was continued during his hospital admission for HIV treatment.

He did require transfer to critical care unit in the setting of worsening fevers, hypotension, and pancytopenia. Increasing concern for IRIS versus HLH prompted initiation of IV dexamethasone. After discussion with hematology and HLH experts, the HLH-94 treatment protocol was initiated. He received dexamethasone taper, slightly modified from the HLH-94 protocol: 10 mg daily for days 1–14; 7.5 mg daily for days 15–28; 5 mg daily for days 29–42; 2.5 mg daily for days 43–49. After an extended multidisciplinary discussion, etoposide was also added. While hospitalized, he received a total of four doses of etoposide (150 mg twice

Table 1
Summary of our patient’s infectious disease testing during hospitalization.
 Abbreviations: MRSA – Methicillin-Resistant *Staphylococcus aureus*; TB – Tuberculosis; AFB – Acid-Fast-Bacilli; NAAT – Nucleic Acid Amplification Tests; CSF – Cerebrospinal Fluid; NTM – Nontuberculosis Mycobacteria; RPR – Rapid Plasma Reagin; VRDL – Viral and Rickettsial Disease Laboratory; BAL – Bronchoalveolar Lavage; HSV – Herpes Simplex Virus; CMV – Cytomegalovirus; EBV – Epstein-Barr Virus; Ag – Antigen; Ab – Antibody..

Bacterial Testing			
Test:	Result:	Test:	Result:
Urinalysis	Negative	Culture, MRSA Nares Screen	Negative
Culture, Bacterial, Blood	Negative	QuantiFERON-TB Gold	Indeterminate
Culture, Stool/Rectal	Negative	Culture, AFB, Blood	Positive (NTM)
Stool WBC	Positive	AFB Culture, CSF	Negative
<i>Chlamydia</i> PCR	Negative	AFB Culture, Bronch	Negative
<i>Gonorrhoeae</i> NAAT	Negative	AFB Culture, Axillary Lymph Node	Negative
RPR	Negative	Culture, Bacterial, Aerobic, Axillary Lymph Node	Negative
Culture, Bacterial, Bronch	Negative	Culture, Bacterial, Anaerobic, Axillary Lymph Node	Negative
Culture, CSF	Negative	BAL Culture, <i>Actinomyces</i>	Negative
CSF VRDL	Negative	BAL Culture, <i>Nocardia</i>	Negative
Viral Testing			
Lab:	Result:	Lab:	Result:
Viral Hepatitis Panel	Negative	HSV I Ab IgM	Negative
EBV PCR	Negative	HSV II Ab IgM	Negative
CMV PCR	Positive	CMV Quantitative PCR	Positive (642 IU/mL; reference negative)
CMV IgG Ab	Positive	CMV IgM Ab	Negative
Fungal Testing			
Test:	Result:	Test:	Result:
<i>Blastomyces</i> Ag, Blood	Weakly Positive	<i>Cryptococcus</i> Ag, CSF	Negative
<i>Histoplasma</i> Ag, Blood	Positive	<i>Cryptococcus</i> Ag, Blood	Negative
<i>Histoplasma</i> Ag, Urine	Positive	<i>Aspergillus</i>	Negative
BAL Culture, Fungal	Positive (<i>Histoplasma capsulatum</i>)	Galactomannan Ag Fungitell	Negative
Parasite Testing			
Test:	Result:	Test:	Result:
<i>Strongyloides</i> IgG Ab	Negative	<i>Toxoplasma gondii</i> PCR	Negative
Ova & Parasite, Stool	Negative	Malaria Smear	Negative
Ova & Parasite, Bronch	Negative		
Other Notable Testing:			
Test:	Result:	Test:	Result:
Respiratory PCR	Negative	Gastrointestinal PCR	Negative
CSF PCR	Negative		

weekly) and was scheduled to receive 6 additional outpatient doses (one dose per week).

Outcome and follow-up

After the initiation of dexamethasone and etoposide per the HLH-94

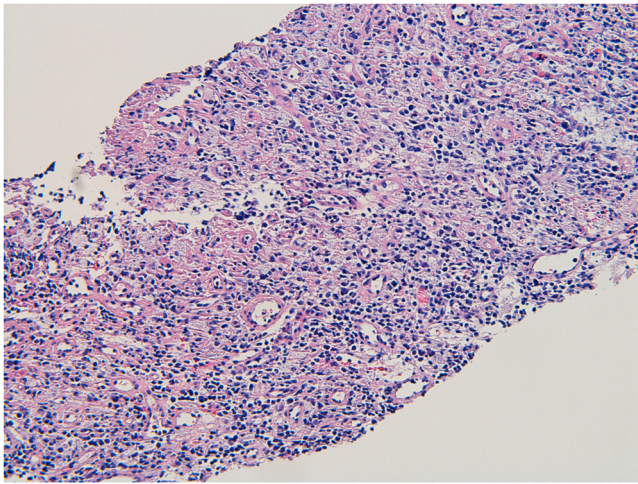


Fig. 1. Axillary lymph node biopsy demonstrating necrotizing lymphadenitis; H&E stain.

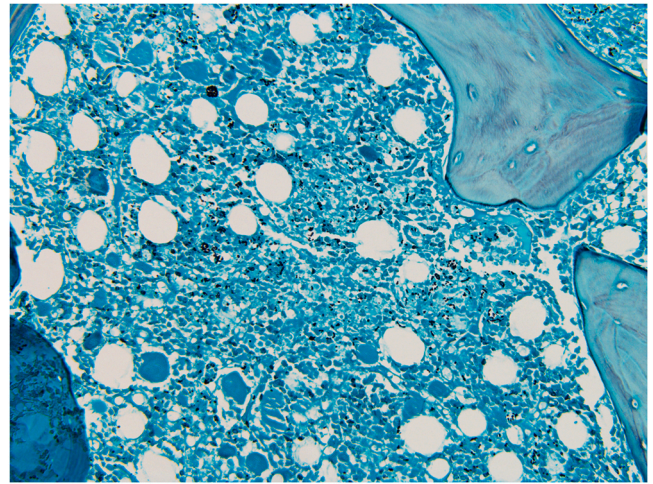


Fig. 4. Bone marrow biopsy demonstrating numerous fungal organisms, consistent with Histoplasma; GMS stain.

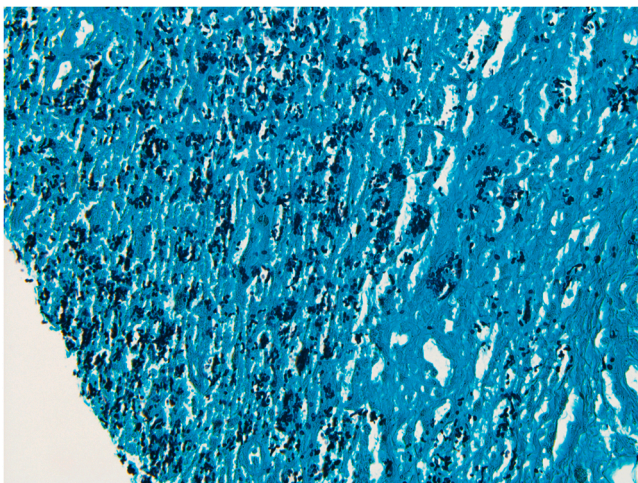


Fig. 2. Axillary lymph node biopsy with numerous fungal organisms present, consistent with Histoplasma; GMS stain.



Fig. 5. Skin lesions on the face consistent with disseminated histoplasmosis.

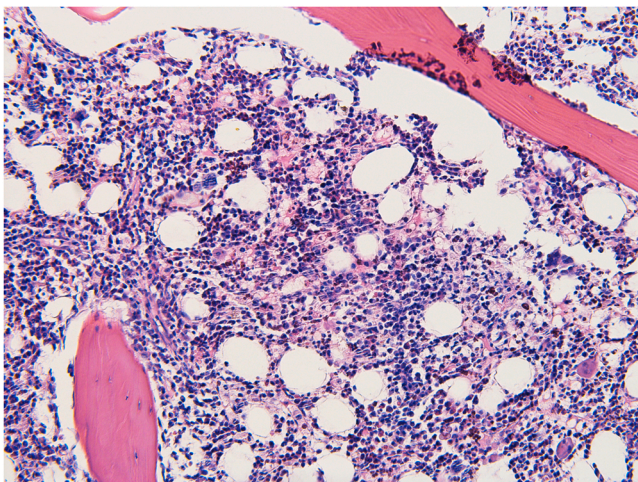


Fig. 3. Bone marrow biopsy with subtle interstitial infiltration of histiocytes; H&E stain.

Table 2
The HLH-2004 diagnostic criteria that our patient met. Abbreviations: NK – Natural Killer; HLH – Hemophagocytic Lymphohistiocytosis.

The diagnosis of HLH can be established by fulfilling either A or B	Criteria Our Patient Met:
A. Molecular diagnosis with HLH-associated genetic mutations	Not Obtained
A. Five of the following eight criteria	
• Fever > 38.5 °C	Present
• Splenomegaly	Present
• Cytopenia of two cell lineages (Hgb <9 g/dL; platelets < 100,000/ μ L; absolute neutrophil count < 1000/ μ L)	Present
• Hypertriglyceridemia (fasting triglycerides > 265 mg/dL) and/or hypofibrinogenemia (fibrinogen < 150 mg/dL)	Not present
• Hemophagocytosis in bone marrow, spleen, lymph node, or liver	Not present
• Low or absent NK cell activity	Not Obtained
• Ferritin > 500 ng/mL	Present
• Elevated soluble CD25 (soluble IL-2 receptor alpha)	Present

protocol, he had resolution of fever, anorexia, diarrhea, and abdominal pain. We monitored daily ferritin levels, weekly IL-2 receptor alpha levels and weekly CMV PCRs. At the time of discharge, his ferritin level had significantly decreased (2310 ng/mL; reference range 28–365). Additionally, his IL-2 receptor alpha level had also decreased (818/mL; reference range 223–710). Response to steroid and etoposide therapy was confirmed by his clinical improvement, decreasing IL-2 receptor alpha levels, and decreasing ferritin levels. He was safely discharged home in stable condition on hospital day 37.

After discharge, growth of non-tuberculous mycobacteria on acid fast blood cultures drawn 5 weeks earlier was reported. As he had already received active agents and was recovering, no further anti-mycobacterials were planned. He continued his clinical improvement as an outpatient and finished etoposide therapy with hematology. He established care with local HIV providers and CD4 count rapidly improved to more than 200 μ L.

Discussion

HLH is a dysregulated immune state defined by natural killer cell and cytotoxic T cell dysfunction, macrophage hyperactivation, and cytokine hypersecretion which leads to diffuse cellular damage and multiorgan failure [1,2,6]. HLH remains a challenging diagnosis for clinicians due to its non-specific clinical presentation that mimics many infections and malignancies [6,7]. HLH often presents as a life-threatening febrile illness that manifests with high-grade fevers, profound cytopenias, hepatosplenomegaly, extreme hyperferritinemia (> 50,000 mg/dL) and diffuse lymphadenopathy. The diagnosis of HLH becomes more challenging in patients living with HIV/AIDS due to their susceptibility to opportunistic infections, risk of IRIS, and complications associated with the initiation of antiretroviral therapy. Without prompt diagnosis and treatment, acquired HLH confers a mortality rate of approximately 40 % [7,8]. As expected, mortality increases in the setting of active HIV. This case highlights the role of treatment of HLH in patients living with AIDS with polymicrobial infections. His remarkable recovery despite AIDS, CMV, NTM bacteremia, disseminated histoplasmosis and HLH is encouraging.

Viral infections, specifically EBV and CMV, are common triggers of acquired HLH [1,9,10]. Less commonly, fungal infections can cause HLH [1,9–11]. Prior cases of HLH secondary to disseminated histoplasmosis have been documented in immunocompromised patients living in *Histoplasma*-endemic areas [12]. Our patient, having lived in endemic areas, presented with symptoms consistent with both HLH and classic disseminated histoplasmosis. Although opportunistic infections are common triggers of acquired HLH, it is important to remember that HIV may trigger HLH, even without known coinfection [10]. Unfortunately for many patients, the signs, and symptoms of typical HLH overlap with the classic signs and symptoms of common opportunistic infections. This case stresses the importance of understanding that patients living with HIV/AIDS can present with multiple opportunistic infections and that many of those infections can trigger HLH.

We utilized the HLH-2004 criteria (Table 2) to establish the diagnosis in our patient despite the absence of molecular testing or pathologic findings of hemophagocytosis on bone marrow biopsies. Although hemophagocytosis is a hallmark of HLH, it is not necessary for diagnosis [7,10]. In acquired, infection mediated HLH, antimicrobial therapy is critical and can eliminate the need for chemotherapeutic medications [10]. However, failure to respond to antimicrobial therapy and clinical deterioration indicate need to initiate HLH-specific treatment [10,13]. Given our patient's viremia and cytopenias, ruxolitinib was initially considered over etoposide. Ruxolitinib has demonstrated a response rate of over 60 % when used in patients with refractory/ relapsed HLH [14]. However, due to socioeconomic circumstances and availability of ruxolitinib we began etoposide. Prior reports have demonstrated the successful use of etoposide in the treatment of HLH in patients living with HIV/AIDS [15,16]. First dose reduction was performed as a

precautionary measure due to his clinical state, cytopenias, and multiple infections. The patient showed excellent response to etoposide: rapid clinical improvement, decreasing IL-2 receptor alpha, and decreasing ferritin.

This case encourages providers to consider HLH as a cause of fever, even in the setting of multiple opportunistic infections. Even more remarkably, it demonstrates the successful use of HLH-94 protocol in the treatment of infection-mediated HLH in the setting of HIV.

CRedit authorship contribution statement

All authors reviewed the literature and helped write the manuscript. Benjamin Fogelson DO, Krupa Patel DO, Jared Spoons DO, Shawna Stephens DO, and Megan Edwards MD performed critical revisions of the article and approved the final version of manuscript.

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None to declare.

Ethical approval

Case report was approved by IRB.

Consent

Obtained.

Conflict of Interest

None to declare.

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