Case report

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

Benjamin Fogelson *, Krupa Patel, Jared Spoons, Shawna Stephens, Megan Edwards *

Department of Medicine, University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

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 non-tuberculous 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 bictegravir, emtricitabine, and tenofovir alafenamide for HIV. His past medical history included malaria as a young child. He denied any surgical history.
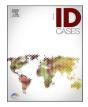
He immigrated to the Southwest United States from Honduras approximately 5 years earlier, and more recently moved the Southeast United States. His social history was also notable for unprotected sex with both male and female partners. On exam he was febrile with a

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

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

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

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

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

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/μL; absolute neutrophil count < 1000/μL)	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 μL.

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.

References

[1] Rouphael NG, Talati NJ, Vaughan C, et al. Infections associated with haemophagocytic syndrome. Lancet Infect Dis 2007;7(12):814–22.

[2] Mehta RS, Smith RE. Hemophagocytic lymphohistiocytosis (HLH): a review of literature. Med Oncol 2013;30(4):740.

[3] Swaminathan N, Vinicius JM, Serrins J. Hemophagocytic lymphohistiocytosis (HLH) in a patient with disseminated histoplasmosis. Case Rep Hematol 2020; 2020:5638262.

[4] Henter JI, Aricò M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study group of the histiocyte society. Med Pediatr Oncol 1997;28(5):342–7.

[5] Ehl S, Astigarraga I, von Bahr Greenwood T, et al. Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: consensus statements by the HLH steering committee of the histiocyte society. J Allergy Clin Immunol Pract 2018;6(5):1508–17.

[6] Castelli AA, Rosenthal DG, Bender Ignacio R, et al. Hemophagocytic lymphohistiocytosis secondary to human immunodeficiency virus-associated histoplasmosis. Open Forum Infect Dis 2015;2(4):ofv140.

[7] Akenroye AT, Madan N, Mohammadi F, et al. Hemophagocytic lymphohistiocytosis mimics many common conditions: case series and review of literature. Eur Ann Allergy Clin Immunol 2017;49(1):31–41.

[8] Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. Rheumatology 2019; 58(1):5–17.

[9] Subedee A, Van Sickels N. Hemophagocytic syndrome in the setting of AIDS and disseminated histoplasmosis: case report and a review of literature. J Int Assoc Provid AIDS Care 2015;14(5):391–7.

[10] Campo M, Berliner N. Hemophagocytic lymphohistiocytosis in adults. Hematol Oncol Clin N Am 2015;29(5):915–25.

[11] Telles JP, de Andrade Perez M, Marcusso R, et al. Hemophagocytic syndrome in patients living with HIV: a retrospective study. Ann Hematol 2019;98(1):67–72.

[12] Asanad S, Cerk B, Ramirez V. Hemophagocytic lymphohistiocytosis (HLH) secondary to disseminated histoplasmosis in the setting of acquired immunodeficiency syndrome (AIDS). Med Mycol Case Rep 2018;20:15–7.

[13] Jabr R, El Atrouni W, Male HJ, et al. Histoplasmosis-associated hemophagocytic lymphohistiocytosis: a review of the literature. Can J Infect Dis Med Microbiol 2019;2019:7107326.

[14] Wang J, Wang Y, Wu L, et al. Ruxolitinib for refractory/relapsed hemophagocytic lymphohistiocytosis. Haematologica 2020;105(5):e210–2.

[15] Macauley P, Abu-Hishmeh M, Dumancas C, Alexander-Rajan V, Piedra-Chavez F, Nada K, et al. Hemophagocytic lymphohistiocytosis associated with parvovirus B19

in a patient with acquired immunodeficiency syndrome. J Invest Med High Impact Case Rep 2019;7:2324709619883698.

[16] Jabr R, El Atrouni W, Male HJ, Hammoud KA. Histoplasmosis-associated hemophagocytic lymphohistiocytosis: a review of the literature. Can J Infect Dis Med Microbiol 2019;2019:7107326.