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Hemophagocytic lymphohistiocytosis (HLH) secondary to disseminated histoplasmosis in the setting of Acquired Immunodeficiency Syndrome (AIDS)

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare and aggressive disease involving immune system over-activation leading to hemophagocytosis. HLH requires early diagnosis and prompt treatment initiation, especially in patients with Acquired Immunodeficiency Syndrome (AIDS). We present a case of a middle-aged male with AIDS and renal failure, who developed HLH secondary to disseminated histoplasmosis. Etoposide chemotherapy as recommended by the HLH 2004 Guidelines was deferred and treatment focused instead on anti-fungal therapy. Anti-retroviral therapy followed thereafter.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by excess immune activation leading to inflammatory cytokine overproduction and hemophagocytosis [1]. Such a phenomenon of hyperinflammation can be either familial or acquired in origin with the most common causes including infection, autoimmune disease, malignancy, and immunosuppression [2]. Acquired HLH, also known as secondary HLH, is an aggressive clinical entity requiring early diagnosis and prompt initiation of appropriate therapies. However, the management approaches for such a fulminant disease remain controversial. In particular, management of HLH secondary to disseminated histoplasmosis is especially not well defined and decisions regarding when to begin immunosuppressive therapy as indicated in the HLH-2004 guidelines are heavily debated [1]. Infection with *Histoplasma capsulatum*, while often asymptomatic, can occasionally lead to severe disease with hematogenous dissemination occurring in approximately 1 in 2000 patients, typically in immunocompromised individuals and the elderly [3]. The most common presenting symptoms in disseminated disease include fever, fatigue, and weight loss and management focuses on rapidly treating the underlying infection with anti-fungal agents [4]. However, the lack of specificity in these presenting symptoms often leads to broad spectrum anti-biotic therapy for presumed sepsis, delaying diagnosis and proper treatment of the underlying infectious [2]. Among patients with Human Immunodeficiency Virus (HIV), HLH is most commonly implicated in the setting of AIDS, permitting opportunistic infection and in turn triggering the onset of HLH [5].

In this report, we present a case of a middle-aged male with no significant past medical history, newly diagnosed Acquired Immunodeficiency Syndrome (AIDS), and renal failure, who developed HLH in the context of disseminated histoplasmosis. The purpose of this article is to raise the index of suspicion for diagnosis of HLH secondary to histoplasmosis with respect to presentation and appropriate diagnostic tests in order permit timely and effective clinical approaches.

2. Case

A 48-year-old man of El Salvadorian descent with a past medical history of gout presented to the emergency department with 6-month history of generalized weakness, decreased appetite, 25-lb unintentional weight loss, and abdominal pain. The patient denied fevers, hemoptysis, recent travel, alcohol, tobacco, or other drug use, dysuria, melena, hematochezia, diarrhea, constipation, or hematuria. On presentation, the patient had a heart rate of 114, temperature of 37.4 °C, respiratory rate of 25 breaths per minute, and an oxygen saturation of 96% on room air. Examination was remarkable for dry oral mucosa, dorsal tongue with brownish discoloration and white plaques bilaterally, mild scleral icterus, mildly tender to palpation of the right upper quadrant on abdominal exam, alert and oriented only to person and place and without focal neurologic deficits. Laboratory test results were notable for aspartate aminotransferase 185 μ/L (reference range

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10–40), alanine aminotransferase 76 μ/L (reference range 7–56), alkaline phosphatase 362 μ/L (reference range 44–147), total bilirubin 4.6 mg/dL (reference range 0.1–1.2), white blood cell count of 4.8 × 10^3/mL (reference range 3.5–10.5 × 10^3) with 53% bandemia (normal ≤ 10), hemoglobin 9.1 g/dL (normal 13.5–17.5), platelet count 33 × 10^3/μL (normal 150–450 × 10^3), and lactate dehydrogenase of 520 units/L (normal 140–280), serum ferritin of 31,855 ng/mL (reference range 20–230 ng/mL), serum fibrinogen of 158 mg/dL (reference range 239–439), serum triglyceride level of 434 mg/dL (reference range 0–150 mg/dL). A computed tomography scan of the chest, abdomen, and pelvis was noted to have small reactive upper abdominal lymph nodes along with a moderate amount of intra-abdominal free fluid and mild hepatomegaly. In addition, a chest x-ray, urinalysis and peripheral blood smear were performed and were normal. The patient was admitted to the inpatient medicine service on 1/23/2017, D0 (day 0), and started on vancomycin, ceftriaxone, azithromycin as well as IV fluids for presumed sepsis. He required broadening to cefepime and flagyl as he was persistently febrile. Given the constellation of clinical and laboratory findings concerning for a hematologic process such as HLH, Hematology consultation was obtained. Further laboratory workup revealed a positive HIV test with CD4 count of 20 (normal 500–1500), soluble CD25 of 2823 (normal 5–398 pM), and elevated urine *Histoplasma* antigen level. On D1, a bone marrow biopsy was performed revealing hemophagocytosis as well as budding yeast on (Fig. 1). At this time, the patient was not started on anti-retroviral medication due to concern of immune reconstitution inflammatory syndrome (IRIS). A lumbar puncture was performed to assess for possible central nervous system involvement and additional opportunistic infections, and was within normal limits. Etoposide was deferred at this time, however, the patient was started on a two-day course of dexamethasone and experienced mild subjective improvement of symptoms. On D2, the patient presented with hemoptysis with platelet count < 20. CT scan of the chest showed miliary histoplasmosis and was ruled out for active TB. He was transfused to maintain the platelet count > 50 and the hemoptysis resolved, having no subsequent episodes. Later that day, the culture obtained from the bone marrow biopsy grew *Histoplasma capsulatum*. With pancytopenia, hemophagocytosis on bone marrow biopsy, elevated CD25, elevated triglycerides, elevated ferritin, and splenomegaly confirmed on abdominal ultrasound, the patient met criteria for HLH in the setting of disseminated histoplasmosis (Table 1). Infectious disease (ID) was consulted, dexamethasone was discontinued and the patient was started on liposomal amphotericin B. The antibiotics were narrowed and eventually stopped on D3. Over the following days (D5-10), the patient continued to have various episodes of fevers, tachycardia and tachypnea. Full fever work up was performed and was overall negative. The patient's sepsis physiology was attributed to a Jarisch-Herxheimer reaction to amphotericin in response to histoplasmosis and was not started on antibiotics. After completing the two-week course of amphotericin (D2-15), the patient showed marked improvement clinically and on subsequent laboratory evaluation including the patient's serum creatinine, downtrending to 1.43 from 4.93 on admission without requiring dialysis. The patient was discharged on itraconazole 200 mg PO BID along with azithromycin and dapsone for prophylaxis of opportunistic infection. The patient was scheduled for close follow up in Infectious Disease Clinic. Initiation of highly active anti-retroviral therapy (HAART) was planned during follow-up in ID Clinic.

Table 1
Diagnostic criteria for HLH [3].

1. Fever
2. Splenomegaly
3. Cytopenias affecting > 2 lineages
a. Hemoglobin < 9 g/dL
b. Platelets < 100 × 10ˆ9/L
c. Neutrophils < 1.0 × 10ˆ9/L
4. Hypertriglyceridemia and/or hypofibrinogenemia
a. Triglycerides ≥ 265 mg/dL
b. Fibrinogen ≤ 150 mg/dL
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK cell activity
7. Ferritin ≥ 500 mg/L
8. sCD25 (ie, sIL2R) > 2400 U/mL

3. Discussion

We presented the case of a male patient with advanced HIV, who developed HLH secondary to disseminated histoplasmosis with proven infection with *Histoplasma capsulatum*.

Given the aggressive and rapidly fatal nature of HLH, prompt diagnosis and treatment are vital for survival as 100% mortality is seen in untreated patients [6]. Poorer prognostic outcomes are especially prevalent in HIV patients with CD4 counts less than 200 cells per μL as seen in our patient [7]. Infection with *Histoplasma capsulatum* commonly occurs from inhaling soil enriched with bird and bat feces. While typically occurring in immunocompromised hosts, HLH secondary to histoplasmosis should also be suspected in immunocompetent patients [6]. However, given the broad range of differential diagnoses for non-specific symptoms such as fever, fatigue, and pancytopenia in an AIDS patient, and the rarity of HLH, especially in the context of HIV, the diagnosis of HLH attributed to secondary causes such as disseminated histoplasmosis is inevitably delayed. In a case presentation reported by Dawn and fellow colleagues, diagnosis of HLH was delayed in a previously healthy 30 year-old woman for a period of 1 month, resulting in progressive HLH and ultimately death despite initiation of therapy upon diagnosis [8]. In addition, a review of 22 histoplasmosis-associated HLH cases demonstrated that of the 7 patients that died, 4 expired prior to initiation of therapy, and the other 3 expired while on treatment with amphotericin B in addition to immunotherapy with intravenous immunoglobulin [1].

Additional obstacles to a timely diagnosis of HLH secondary to disseminated histoplasmosis include the presentation of HLH secondary to HIV alone, in the absence of opportunistic infection [9]. Prior to

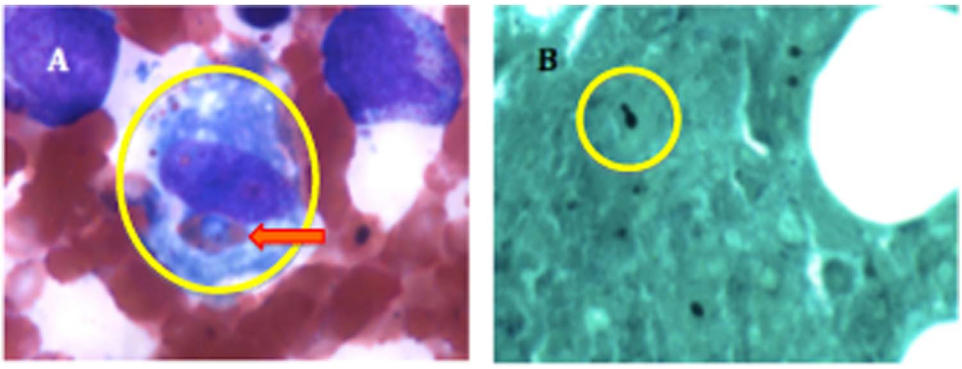

Fig. 1. Wright-Giemsa stains illustrating (A) macrophage (yellow circle) with red blood cells (red arrow) in the cytoplasm, consistent with hemophagocytosis; (B) budding yeast forms (yellow circle) characteristic of *Histoplasma capsulatum*.

Table 2
Laboratory values on initial presentation and following anti-fungal therapy.

Labs	On admission (D0)	Post-amphotericin areatment (D15)
Hemoglobin (g/dL)	9.1	12.4
WBC count (k/uL)	4.8	4.8
Platelet (k/uL)	33	228
Fibrinogen (mg/dL)	158	378
Ferritin (ng/mL)	31,855	694
Triglycerides (mg/dL)	434	135

initiation of antiretroviral therapy, clinical features such as fever, splenomegaly, pancytopenia, hypertriglyrecidemia, and hyperferritinemia are commonly featured in patients with AIDS [10]. This was illustrated in a case series of 56 patient autopsies, 54 of which consecutively had AIDS and 11 were confirmed to have hemophagocytosis [11].

Identifying the underlying insult for trigger HLH is critical for determining which therapeutic route to pursue. In the case of HLH solely secondary to HIV, effective recovery has been reported to follow prompt initiation of HAART [12,13], while successful treatment for HLH secondary to Epstein-Barr virus (EBV) entails immunosuppression therapy alone [1], and infection with bacterial or fungal agents should focus on directly treating for the underlying pathogen with anti-microbials.

The Histiocyte Society has provided guidelines outlining the criteria for diagnosis and management for HLH accordingly, however, these algorithms have been largely extrapolated from pediatric populations featuring familial conditions, autoimmune disorders, and malignancy [14–16]. In turn, studies demonstrating the applicability of these criteria for diagnosis and treatment to adult patients in the context of HIV are largely lacking and are of vital necessity [3].

As suggested in the Histiocyte Society HLH-2004 guidelines, the current standard of managing HLH entails initiating cytotoxic chemotherapy and prospective bone marrow transplant for patients exhibiting severe or relapsing HLH [14–16]. In our case presentation, however, these recommendations were deferred and treatment largely focused on addressing the underlying trigger for HLH. In the previously mentioned review of 22 histoplasmosis-associated HLH cases, of the 10 patients that received amphotericin B only, all of them survived, while 3 our of 4 patients that received immunotherapy with intravenous immunoglobulin (IVIG) died [1]. This suggests that in the context of timely diagnosis and prompt treatment, management with chemotherapy and bone marrow transplantation as suggested in the guidelines may not be required and treatment should focus on addressing the underlying infectious agent. Such a therapeutic approach is supported by the follow up labs obtained for our patient case (Table 2). In particular, the patient exhibited significant improvement and normalization of hemoglobin, platelets, fibrinogen, ferritin, triglyceride level, no longer satisfying the objective criteria for HLH.

In conclusion, this case demonstrates the importance of searching for secondary causes of HLH in adults, as the majority of adult HLH cases are secondary to an underlying trigger, 41.1% of which are triggered by infection and 38.8% by malignancy [17]. As a result, the optimal treatment of adult HLH depends on targeting the underlying biological insult, which may vary from patient to patient. Additionally, this case demonstrates the need to consider histoplasmosis as a secondary cause of HLH in adults, especially in patients with advanced HIV. Our case presentation highlights the importance of having a raised awareness for HLH in patients with persistent constitutional symptoms such as fever, fatigue, and weight loss. In such cases where the origin of fever is unknown, especially in patients with AIDS, early assessment of serum ferritin level in conjunction with appropriate biopsy and microbiology testing is vital [3].

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Conflict of interest

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