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 antifungal 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 antifungal 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 μL (reference range...
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 blood smear were performed and were normal. The patient was admitted on vancomycin, ceftriaxone, azithromycin as well as IV fluids for presumed sepsis. He required broadening to cefepime and treatment with amphotericin B in addition to immunotherapy with intravenous immunoglobulin. 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 soluble CD25 of 2823 (normal 5–398 pM), and elevated urine

Table 1
Diagnostic criteria for HLH [3].

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

on admission without requiring dialysis. The patient was discharged on intravenous immunoglobulin (IVIG) 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.

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.](image-url)
initiation of antiretroviral therapy, clinical features such as fever, splenomegaly, pancytopenia, hypertriglyceridemia, and hyperferritinaemia 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 out 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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References

[1] A.A. Castelli, D.G. Rosenthal, R.B. Ignaico, Hemophagocytic lymphohistiocytosis secondary to human immunodeficiency virus-associated histoplasmosis, Open Forum Infect. Dis. 2 (4) (2015) ofv146.
[2] S.B. Kim, A rare case of acquired immune deficiency syndrome related pancytopenia, Hematol. Rep. 7 (2015) 5475.
[3] A.L. Colombo, A. Tobón, A. Restrepo, F. Quesada-Telles, M. Nucci, Epidemiology of endemic systemic fungal infections in Latin America, Med. Mycol. 49 (8) (2011) 785–798.
[4] L.J. Wheat, Improvements in diagnosis of histoplasmosis, Expert Opin. Biol. Ther. 6 (11) (2006) 1207.
[5] A. Subedi, N. Van Sickets, Hemophagocytic syndrome in the setting of AIDS and disseminated histoplasmosis: case report and a review of literature, J. Int. Assoc. Provid. AIDS Care 14 (5) (2015) 391–397.
[6] S. Saluja, S. Sunita, S. Bhasin, D.K. Gupta, B. Gupta, S.P. Kataria, et al., Disseminated histoplasmosis with reactive haemophagocytosis presenting as PUD in an immunocompetent host, JAPI (2005) 53.
[7] M. Gotoh, J. Matsuda, K. Gohchi, Successful recovery from human immunodeficiency virus (HIV)-associated haemophagocytic syndrome treated with highly active anti-retroviral therapy in a patient with HIV infection, Br. J. Haematol. 112 (2001) 1090.
[8] D. Ng, N. Ghooh, L.K. Hicks, Hemophagocytic lymphohistiocytosis – late diagnosis in an adult patient, BMJ Case Rep. (2009).
[9] J.W. Verbsky, W.J. Grossman, Hemophagocytic lymphohistiocytosis: diagnosis, pathophysiology, treatment, and future perspectives, Ann. Med. 38 (2006) 20–31.
[10] T. Doyle, S. Bhagani, K. Cwynarski, Haemophagocytic syndrome and HIV, Curr. Opin. Infect. Dis. 22 (1) (2009) 1–6.
[11] G.W. Niedt, R.A. Schinella, Acquired immunodeficiency syndrome clinicopathologic study of 56 autopsies, Arch. Pathol. Lab. Med. 109 (8) (1985) 727–734.
[12] C. Castilletti, R. Preziosi, G. Bernardini, et al., Hemophagocytic syndrome in a patient with acute human immunodeficiency virus infection, Clin. Infect. Dis. 38 (2004) 1792–1793.
[13] L.S. Chen, W.W. Wang, T.J. Chiuo, Hemophagocytic syndrome: an unusual manifestation of acute human immunodeficiency virus infection, Int. J. Hematol. 78 (2003) 450–452.
[14] J.J. Henter, A. Horne, M. Arico, HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis, Pediatr. Blood Cancer 48 (2) (2007) 124–131.
[15] J.J. Henter, M. Arico, R.M. Egele, et al., HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis, Med. Pediatr. Oncol. 28 (1997) 342–347.
[16] J.J. Henter, G. Elinder, A. Ost, Diagnostic guidelines for hemophagocytic lymphohistiocytosis, The FHL study group of the histiocyte society, Semin. Oncol. 18 (1) (1991) 29–33.
[17] P. La Rosse, Treatment of hemophagocytic lymphohistiocytosis in adults, Am. Soc. Hematol. 1 (2015) 190–196.