Annals of Case Reports
Bionghi N, et al. Ann Case Rep: 11: 102530
www.doi.org/10.29011/2574-7754.102530
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Case Report

From Spores to Solutions: Untangling the Treatment Enigma of Histoplasmosis Associated HLH

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Citation: Bionghi N, Mehta R. (2026). From Spores to Solutions: Untangling the Treatment Enigma of Histoplasmosis Associated HLH. Ann Case Report. 11: 2530. DOI: 10.29011/2574-7754.102530

Received: 07 February 2025; **Accepted**: 11 February 2026; **Published**: 16 February 2026

Abstract

Disseminated histoplasmosis is highly fatal and can result in histoplasmosis associated hemophagocytic lymphohistiocytosis (HA-HLH). In this case report, we describe a critically ill patient with HIV/AIDs and HA-HLH. She improved with antifungal therapy and steroids for presumed HA-HLH. Optimal therapy for HA-HLH has not been identified and warrants further study.

Keywords: Histoplasma Capsulatum; Histoplasma; Hemophagocytic Lymphocytosis; Malignancies.

Introduction

Histoplasma capsulatum is a fungal organism present in soil that causes the granulomatous disease histoplasmosis upon inhalational exposure. There are multiple variants of Histoplasma: variants capsulatum and duboisii are the most common [1] with capsulatum the most common variant globally. Histoplasmosis is a ubiquitous fungus that has been found on every continent, most recently in Antarctica in penguin excreta [2]. Mortality with histoplasmosis infection is higher in patients with human immunodeficiency virus (HIV) [3-5].

Hemophagocytic lymphocytosis (HLH) is a complex syndrome causing uncontrolled proliferation of lymphocytes and activation of IFN-y, leading to macrophage activation and subsequent release of inflammatory cytokines. The macrophages infiltrate multiple organs with a tropism to the bone marrow promoting hemophagocytosis. There is limited data on the optimal treatment of HA-HLH. It becomes challenging to diagnose HLH as the clinical manifestations can mimic septic shock and infection itself [6-7]. Primary HLH is the inherited form of the disease, affecting children in the presence of genetic disorders. Secondary HLH is more common than primary and manifests mostly in adults with infections or immune dysregulations as seen in malignancies (T cell lymphomas), rheumatologic disease (Still's disease, lupus), or immunodeficiency disease. Multiple viral, bacterial and fungal infections have been associated with secondary HLH. Histoplasmosis associated hemophagocytic lymphohistiocytosis (HA-HLH) is a rare phenomenon and thought to be <1% of cases [10]. Here we report a case of a young woman living with HIV/AIDS who presented with disseminated histoplasmosis, found to have HA-HLH.

Case Presentation

A 23-year-old female living with HIV, off anti-retroviral medication, was admitted to our medical intensive care unit for acute hypoxemic respiratory failure and shock requiring norepinephrine infusion at 0.2 mcg/kg/minute and vasopressin at 0.03units/min. She required intubation in the emergency department. Prior to intubation, the patient reported a subacute history of fevers after moving from El Salvador to the United States six months prior. Her chest imaging was notable for diffuse airspace opacities and ground glass opacities. A high positive end expiratory pressure (PEEP) strategy of 14 on the ventilator, deep sedation to RAAS -4, paralysis with cisatracurium drip, and inhaled nitric oxide at 20 ppm were immediately initiated on arrival to the MICU. Proning was discussed but given her hemodynamic instability with high two-

pressor requirements, was deferred. She was started empirically on vancomycin, piperacillin-tazobactem, amphotericin at 3 mg/kg every 24 hours, and treatment dose of intravenous trimethoprim/sulfamethoxazole 5 mg/kg every 8 hours. A normal echo, no edema on physical exam, and a normal NT-proBNP argued against volume overload as etiology for her respiratory failure.

Etiologies for her respiratory failure were felt to be PJP, disseminated fungal disease (histoplasmosis vs aspergillosis), disseminated mycobacterial disease, pulmonary hemorrhage from Kaposi's, viral infection, or bacterial infection. Her full respiratory viral panel was negative. Infectious diseases consultants tailored her therapy to doxycycline, piperacillin-tazobactem, amphotericin and trimethoprim/sulfamethoxazole.

Her initial complete blood count was notable for white blood cell count of 13,650, hemoglobin of 8.37, platelets of 84,000 with a neutrophil predominance (she was NOT neutropenic) and 1% eosinophils. Her admission complete metabolic panel was notable for a potassium of 5.0, bicarbonate of 10, and normal creatinine of 0.84 with a lactate of 5.1. Strikingly, her aspartate aminotransferase was 459, alanine transaminase was 85, alkaline phosphatase was 1060, and total bilirubin was 1.6. She was found to have a CD4 count of 86 with viral load of 644,000 and a CD 4 percentage of 11%. Serum strongyloides antibodies were negative. Her urine histoplasma antigen was positive at >24.0. Her fungal complement fixation (CF) showed a 1:64+ titer of histoplasma. Serum fungitell was weakly positive at 89 but other fungal antibodies negative. Her microbiologic testing is summarized in (Table 1). Liver biopsy and bone marrow biopsy were deferred due to her critical illness. There was concern for hepatic involvement with histoplasmosis, although we do not have liver biopsy proven evidence of this. Her cutaneous rash was biopsied and positive for histoplasmosis and she was diagnosed with histoplasmosis disease.

Test	Result
Legionella urine Antigen	Negative
Urine histoplasma Antigen	Detected, >24
Fungitell	89
T spot	Negative
PJP DFA (sputum)	Negative
Respiratory viral pathogen panel	Negative
MRSA nares swab	Negative
Rickettsial RMSF antibodies	Negative, <1:64
Fungal blood culture	Histoplasma capsulatum
Fungal complement fixation CF) antibodies, serum	Histoplasma mycelia CF 1:64
Skin Rash Punch biopsy culture	Histoplasma Capsulatum
Serum Cryptococcal Antigen	Negative
Sputum MTB PCR (x3)	Negative
AFB sputum (x3)	Negative
Fungal culture tracheal aspirate	No fungal growth
Sputum culture with gram stain	Many white blood cells, many yeast
Urine culture	No growth
Blood culture (x2)	No growth
HSV 1 & 2 mons pubis lesion	HSV 2 detected
Stool culture	Negative
Bronchoscopy studies - BAL	
Fungitell	>500
Aspergillus galactomannan	0.8

Nocardia culture	No growth
Legionella culture	No growth
Fungal culture	Intracellular yeast forms of *Histoplasma*
AFB smear with culture	Smear and culture negative
Bacterial Culture	Many WBCs, no growth
Viral culture	Negative
PJP DFA	Negative
Cytology	Negative for malignancy

Table 1: Patient's microbiology is summarized.

With her liver function test abnormalities and HIV, there was concern for HLH with a cytokine inflammatory storm picture. Blood work showed marked serum ferritin elevation at 29,395 ng/mL, and her IL-2 receptor (soluble CD25) was also high at 40260.6 pg/mL. Fibrinogen was 218 mg/dL, triglycerides were 413 mg/dL, and NK cell activity was 8 LU30 (normal). There was substantial hepatomegaly and splenomegaly noted on CT abdominal imaging. The shock was ultimately felt to be septic from histoplasmosis with an inflammatory HLH component. After a multidisciplinary discussion with our HLH taskforce, empiric methylprednisolone 40mg every 12 hours was started for presumed HLH within 24 hours of admission.

Within three days of admission, her oxygenation improved and she was able to undergo a bronchoscopy with bronchoalveolar lavage (BAL). Airway inspection was not concerning for Kaposi's sarcoma. BAL PJP PCR was negative, BAL fungitell was >500. BAL culture grew histoplasmosis capsulatum (Table 1) and she was diagnosed with disseminated histoplasmosis with cutaneous and pulmonary involvement with suspected hepatic involvement although she never received a liver bipsy. She continued to have clinical improvement and was successfully extubated after 13 days of intubation. Lumbar puncture was deferred as her mental status was normal post-extubation and MRI of the brain was without gross nodules or leptomeningeal enhancement. She received two weeks of amphotericin 3 mg/kg and then transitioned to itraconazole for a planned prolonged therapy of 12 months. She survived her hospital stay, started antiretroviral therapy, and was successfully discharged.

Discussion

Clinical manifestations of pulmonary histoplasmosis include fevers, chills, malaise, cough dyspnea and chest pain. Imaging can show diffuse reticulonodular infiltrates often coalescing into discrete areas of consolidation or ground glass opacities. Mediastinal and hilar lymphadenopathy are not ubiquitous. ARDS and HA-HLH can develop within days of symptom presentation. In their case series, Townsend et al [11] identified that the urine Histoplasma antigen was the most consistent diagnostic finding. 7/11 had positive fungal blood cultures for Histoplasma capsulatum, and the most common chest-imaging finding was bilateral infiltrates.

The gold standard of diagnosis of histoplasmosis involves culture of infected tissue and identification of the organism with histopathology and staining. Itraconazole can be used for treatment of mild disease, although IDSA guidelines advise prompt liposomal amphotericin B for moderate to severe infection. [9]

Disseminated histoplasmosis is defined as the presence of disease in two or more organs and is more commonly seen in immunocompromised patients, particularly those with T-cell malfunction/deficiencies, (e.g. patients with HIV/AIDS). Infection by histoplasmosis is dependent on T-cell mediated immunity and this is especially relevant as it is postulated that development of HLH may also be related to abnormal T cell immunity. [6, 9] It was thought that our patient's HIV positivity predisposed her to HA-HLH. An impairment in T cell immunity seems to be the unifying similarity in HIV, histoplasmosis, and HLH.

Per the HLH 2004 guidelines, there are eight diagnostic criteria for diagnosing HLH, and at least five criteria must be present to diagnose HLH [13] Our patient met 6/8 of the 2004 HLH criteria (diagnostic for HLH) and her H score (a validated scoring system for HLH) was 243, which is associated with a >99% probability of HLH.

Treatment of HA-HLH

To date, there are no established treatment guidelines for HA-HLH given the lack of randomized control trials studying this, but the general consensus is that addressing the underlying trigger and controlling the resultant overactive immune system is paramount. This can be done with simply treating the primary etiology or in combination with steroids or other forms of immunosuppression

(including chemotherapy agents such as etoposide, rituximab, IVIG). Studies have suggested that if a treatable trigger is identified early in the diagnosis of HLH and treated in a timely manner, HLH-directed therapy (etoposide and dexamethasone) may not be required.

Most treatment guidelines for patient with refractory HLH stem from the HLH 94 and HLH 2004 studies. HLH 94 was a pediatric study of patients who were less than 16 years of age, had no malignancy, immunodeficiency, or chronic illness. HLH 94 protocol included an 8-week induction of dexamethasone (this form of steroid was chosen given its ability to cross the blood brain barrier) and etoposide with the addition of intrathecal MTX in the presence of CNS symptoms. This regiment resulted in decreased mortality from HLH but a high rate of relapse [14]. The HLH 2004 study was a followup from the HLH-94 study and included the addition of cyclosporine in the induction phase [13]. Major limitations of both those studies were that the patient population the protocols were studied were in children, more of whom had familial etiologies of HLH (less secondary HLH) and they excluded patients with malignancy, immunodeficiency or chronic illness. This severely limits the generalizability of those treatment algorithms to our patient who was an adult living with an untreated chronic illness and was immunocompromised due to her HIV/AIDS status.

In our patient, Methylprednisolone was started within 24 hours of arrival to the hospital for presumed HLH. The multidisciplinary HLH taskforce evaluated the case and the conclusion was to start Methylprednisolone as the sole agent at that early time course of her hospitalization as they were unclear if the HLH findings were from infection (histoplasma serology had not returned yet) or driven by uncontrolled HIV/AIDs. They postulated that if this was secondary HLH associated with HIV or secondary HLH associated from an infection, our patient may not need chemotherapeutic agents if the patient improved with treatment of underlying etiology in a timely manner, however, they did want to use methylprednisolone to mitigate the inflammatory portion of the shock due to HLH. The plan amongst the HLH Taskforce at our institution was if the patient did not clinically improve by the benchmark 48 hours [7], they would have added etoposide to her HLH treatment algorithm. However, the patient began to show signs of improvement in 36 hours and escalation of HLH specific treatment was deferred.

A case series and review of literature by Jabr et al. has suggested that the most common underlying condition associated with HA-HLH is HIV (61% of cases) with a median CD4 count of 17 cells/uL. [7] The majority of patients with HLH do have dissemination. It was reported that the inpatient fatality of HIV patients with HA-HLH was 37%. In this case series, the mortality of HA-HLH was 20% in patients who received Amphotericin + steroids and etoposide +/- cyclophosphamide, 25% in patients who received amphotericin B only, 31% in patients who received steroids and amphotericin, 62% in patients who received IVIG + amphotericin B. One patient received anakinra, IVIG and amphotericin B and survived. The authors postulated that if treatment for histoplasmosis alone does not cause clinical improvement after 48-72 hours, clinicians should consider initiation of treatment for HLH, although the ideal regimen has not been determined.

Another case series of 10 patient with HA-HLH was published in 2015[11]. In this Series, 5/11 patients received concomitant immunosuppression with amphotericin. 2 patients received prednisone only, 1 patient received prednisolone and tacrolimus, one received IVIG and prednisone, one received IVIG only). Of the patients that received any form of immunosuppression, there was an 80% mortality (4/5 died). Out of the group of 5 patient that did not receive additional immunosuppression, 2 died, a 40% mortality. However, this case series was underpowered due to the small number of patients studied, making it difficult to draw conclusions about significant differences in mortality. It is also important to note that patients requiring immunosuppression may serve as surrogates for those with more severe illness, which could contribute to their higher mortality due to the refractory nature of their disease.

Conclusion

Here we present a case of a critically ill patient with respiratory failure and shock due to disseminated histoplasmosis and HA-HLH. This is an under-reported disease process in which empiric and early treatment with liposomal amphotericin B is paramount. Our patient survived after early initiation of liposomal amphotericin B, and solumedrol for HA-HLH.

HA-HLH is a complex disease process and the optimal therapy has not been defined. The treatment for HA-HLH is likely as complex as the disease process itself and must be tailored to the patient's unique clinical situation. However, if there is no clinical improvement after 48-72 hours of standard therapy treating the trigger, it may be reasonable consider adding immunosuppressive agents to help control the overactive immune response. Although the optimal regiment has not been identified, a combination of etoposide and dexamethasone may be the best initial therapies to consider. More study in this complex disease process that intersects the fields of critical care, infectious diseases, immunology, rheumatology and hematology must be done.

Conflict of interests: Neither Dr. Bionghi nor Dr. Mehta have any conflict of interests to report.

Funding: Neither Dr. Bionghi nor Dr. Mehta have any funding sources to report.

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