LETTER TO THE EDITOR

WILEY

Rare case of secondary hemophagocytic lymphohistiocytosis in a patient with disseminated histoplasmosis

To the editor:

A previously healthy 3-month-old male presented to his pediatrician with an isolated fever for a few days. A complete blood count (CBC) revealed hemoglobin (Hb) 81 g/L, mean cell volume (MCV) 79 fl, white blood cell count (WBC) 1.9×10^9/L, absolute neutrophil count (ANC) 3.2×10^9/L, and platelet count 260×10^9/L. Repeated CBC a few days later showed worsening of the leukopenia and anemia.

Upon hospital admission, the patient had a history of fever and lethargy for 11 days. Further history revealed that his father is a farm worker. Initial physical examination showed massive hepatosplenomegaly. Laboratory testing showed pancytopenia and mild elevation of his liver enzymes with Hb 78 g/L, MCV 80 fl, WBC 1.1×10^9/L, ANC 1.2×10^9/L, and platelet count of 110×10^9/L. Abdominal computer tomography confirmed the hepatosplenomegaly. Additional laboratory tests showed ferritin 830 ng/ml, fibrinogen 1.32 mg/L, triglycerides 2.13 mg/L, soluble interlukin-2 (IL-2) receptor 9560 Units/ml, and negative human immunodeficiency virus (HIV) serology.

Histologic examination of the bone marrow showed many activated macrophages and evidence of hemophagocytosis. Further evaluation of the bone marrow sample demonstrated fungal elements characteristic of *Histoplasma capsulatum*. Serum and urine antigen assays were positive for *H. capsulatum*. Cerebral spinal fluid was negative for Histoplasma antigen. Based on clinical and laboratory findings, the patient was diagnosed with disseminated *H. capsulatum* with secondary hemophagocytic lymphohistiocytosis (HLH). Intestinal involvement of the disseminated histoplasmosis was not investigated as there were no associated symptoms.

Treatment was started with intravenous Amphotericin B (AmB) through a peripherally inserted central catheter PICC line for 14 days, followed by a course of oral Itraconazole, as recommended by the Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007.[1] No treatment was started that would target the HLH directly. The patient became afebrile 36 hours after the first dose of AmB and was discharged 5 days later. He was followed closely at the pediatric Hematology-Oncology outpatient. He continued to remain afebrile throughout the entire course of treatment. All cell lines gradually recovered. Urine histoplasma antigen was negative after three months of treatment. Soluble IL-2 levels were obtained every 2 to 4 weeks until levels were within normal limits. The patient continues to remain healthy 24 months post his initial presentation.

HLH is a syndromic condition caused by an overwhelming inflammatory response. It is associated with an outpouring of cytokines and inappropriate activation of the macrophage system, which can cause severe morbidity and possible death.[2] HLH is either a familial condition or secondary to other conditions such as oncologic, infectious, or rheumatologic conditions. The diagnosis of HLH is made by meeting five of eight criteria defined in the HLH-2004 trial, including either specific molecular markers consistent with the diagnosis or fever ≥38.5°C, splenomegaly, cytopenias, hypertriglyceridemia, hemophagocytosis, low or absent natural killer (NK) cell activity, elevated ferritin, and elevated sCD25.[3] HScore is an alternative way to diagnose HLH utilizing nine variables, including clinically known underlying immunosuppression, high temperature, organomegaly, triglyceride, ferritin, serum glutamic oxaloacetic transaminase, and fibrinogen levels, cytopenia, the presence of hemophagocytosis features on bone marrow aspirate.[4] The most common infectious cause of secondary HLH is Epstein–Barr virus. Other infectious causes have been reported, including cytomegalovirus,

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parvovirus B19, HIV, HHV-6, toxoplasmosis, malaria, and *Histoplasma*.[5]

Primary HLH is treated with dexamethasone, methotrexate, and etoposide following the HLH-2004 algorithm, but there is still no consensus on the proper treatment protocol for secondary HLH.[4] Prompt identification and treatment might prevent poor outcomes.

H. capsulatum is a fungus endemic to the Mississippi and Ohio River valleys. It is found in caves and soil contaminated by bird and bat droppings.[6] *H. capsulatum* most commonly causes an asymptomatic pulmonary infection.[6] Disseminated histoplasmosis is a rare complication of an *H. capsulatum* infection, typically seen in the immunocompromised or extremes of age.[1] Treatment of disseminated histoplasmosis differs depending on whether it is a mild or moderate to severe disease. It includes itraconazole for the former and AmB, followed by a course of itraconazole for the latter.[7] If left untreated, it can develop into a secondary HLH. Research on disseminated histoplasmosis with secondary HLH is limited to case reports.

Disseminated histoplasmosis is a difficult diagnosis to make, especially in a non-immunocompromised, healthy patient. It is common for patients in the Midwestern United States to be asymptomatically infected with *H. capsulatum*. The disseminated form of the infection is rare, occurring in less than 1% of patients.[1] Of the small number of cases of disseminated histoplasmosis that do occur, few develop into a secondary HLH.

Secondary or reactive HLH is a challenging phenomenon. No standardized protocol states whether treatment should begin with treating the underlying cause, treating the HLH, or treating both conditions simultaneously. Jordan et al.[8] suggest that all patients with HLH, regardless of whether it is primary or secondary HLH, should be started on the initial therapy guidelines outlined in their article, except for autoimmune disease or malignancy causing secondary HLH. If we were to use this suggestion in our patient, we would have started our 3-month-old patient on dexamethasone and etoposide therapies as well as AmB.[8]

The limited literature that discusses disseminated histoplasmosis with secondary HLH is in those who are immunocompromised.[9] Our patient was healthy prior to this infection. With this in mind, we only started treatment with antifungal therapy and monitored him closely in the intensive care setting for a response. The patient responded almost immediately, returning to an afebrile state in under 2 days. We were able to spare him exposure to high doses of etoposide and dexamethasone and their side effects, including, but not limited to, myelosuppression, peripheral neuropathy, osteoporosis, and hepatotoxicity.

Through this case, we suggest that treatment should begin with treating the infection in patients with disseminated histoplasmosis with secondary HLH without underlying immunosuppression. The patient should be observed to ensure the resolution of both conditions. If no adequate response is obtained with antifungal therapy alone, adjunct therapy with dexamethasone and etoposide should be started. Additional research should focus on defining an adequate response to antifungal therapy and expanding treatment protocols for other infectious etiologies of HLH.

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CONSENT FOR PUBLICATION

The parents of the patient have given written informed consent.

CONFLICT OF INTEREST

None.

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