Case Report

Hemophagocytic Lymphohistiocytosis due to Disseminated Histoplasmosis in a Patient with HIV Infection

Krishna Divyashree, Harpreet Singh, Mayur Parkhi[1], Indrani Karmakar[2], Man Updesh Singh Sachdeva[2], Vikas Suri, Ashish Bhalla

Departments of Internal Medicine, [1]Histopathology and [2]Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract

Hemophagocytic lymphohistiocytosis is usually considered a rapidly progressive fatal illness with poor outcomes. It is of two types: primary or familial and secondary. In patients with HIV, opportunistic infections are the secondary triggers of HLH. First line of management of infection associated HLH is treatment of the underlying infection. Here, we present a case of HLH in HIV infection due to disseminated histoplasmosis managed with liposomal amphotericin B, who required immunosuppressive therapy with intravenous immunoglobulin and dexamethasone due to nonresponse to primary therapy.

Keywords: CD4 count, disseminated histoplasmosis, hemophagocytic lymphohistiocytosis, HIV, *Mycobacterium tuberculosis,* pyrexia of unknown origin

Introduction

Disseminated histoplasmosis is one of most common fungal infections in patients with HIV. Typical patients present with prolonged fever, oral ulcers, gastrointestinal symptoms, cytopenias, and jaundice. Hemophagocytic lymphohistiocytosis (HLH) can be rapidly progressive illness with grave outcomes. Various causes of HLH in patients with HIV include infections like histoplasmosis, tuberculosis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), atypical mycobacterial infection, or hematological or solid malignancies. Disseminated histoplasmosis has been known to cause HLH in patients HIV, especially young males with very low CD4 counts with high mortality. Most of the patients respond to intravenous antifungals alone. Despite effective antifungal therapies, mortality is still high. Some patients may require immunosuppression in the form of steroids and intravenous immunoglobulins.

Case Report

A 30-year-old female with a history of HIV for 8 years and poor compliance to treatment was admitted with high grade intermittent fever up to 102° F for 6 weeks, 5-6 episodes of non-bloody loose stools for 3 weeks without pain abdomen or tenesmus; and altered behaviour for 1 week. She had lost 12 kg over last 2 months. Evaluated in outpatient clinic; her CD4 count was 25/μL and stool examination showed *Entamoeba histolytica*; she received nitazoxanide, fluconazole, and azithromycin. However, she was admitted for persistent symptoms; on examination, she had blood pressure of 112/74 mm of Hg, pulse of 128 per min, respiratory rate of 18 per min, pallor, oral ulcers, and bilateral firm nontender inguinal lymphadenopathy of 2 cm × 2 cm. Routine investigations revealed hemoglobin of 3.4 g/dl, total leukocyte count of 4200/mm^3, and platelets count of 53000/mm^3 along with aspartate transaminase of 338 U/L (range, 2–40 U/L), alanine transaminase of 37 U/L (range, 2–41 U/L), and serum albumin of 1.99 gm/L (range, 3.4–4.8 g/dL). She received three units of packed red blood cell transfusions in hospital. Repeat stool examination was normal for atypical organisms. She had raised serum LDH (lactate dehydrogenase) of 2420 U/L and serum ferritin of 18,874 ng/ml (range for diagnosis in HLH >500 ng/ml). In patients with such a low CD4 count and

Address for correspondence: Dr. Harpreet Singh, Department of Internal Medicine, 4th Floor, Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India.
E-mail: hs.30.singh@gmail.com

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uncontrolled primary disease, various possibilities were kept like disseminated fungal infection, disseminated tuberculosis, CMV infection, drugs, hemophagocytic lymphohistiocytosis, or malignancy. Contrast-enhanced computed tomography of the chest and abdomen revealed enlarged liver and spleen and lymphadenopathy with multiple hypodense lesions in liver and spleen without pulmonary involvement. Inguinal lymph node biopsy [Figures 1 and 2] and bone marrow biopsy revealed PAS stain positivity suggestive of histoplasmosis [Figures 3 and 4] with GeneXpert for *Mycobacterium tuberculosis* being negative in both. Liposomal amphotericin B as per weight (3 mg/kg/day) was started in view of disseminated histoplasmosis. There was no improvement in cytopenias and elevated transaminases after 3 days of amphotericin B with worsening leucopenia (800/mm^3) and thrombocytopenia (20000/mm^3). Workup for Hepatitis A, B, C, E, CMV, and EBV were negative. Possibility of secondary hemophagocytic lymphohistiocytosis was also considered with persistently raised serum ferritin of 19114 ng/ml (>500 ng/ml), low fibrinogen of 1.37 gm/L (≤1.5 gm/L), and worsening leucopenia and thrombocytopenia (≥2 cell lineages) with H score of 208 (88%–93% probability). She was started on intravenous immunoglobulin 1.5 g/kg, but has to be shifted to oral dexamethasone in view of financial constrains; she had improvement in her cytopenias, liver enzymes, and reduction of ferritin levels. She received 2 weeks of liposomal amphotericin B and later on changed to oral itraconazole 200 mg three times a day with start of antiretroviral therapy (tenofovir/lamivudine/dolutegravir) and was discharged. At follow-up visit after 2 months, she was free of all symptoms with normalization of laboratory parameters.

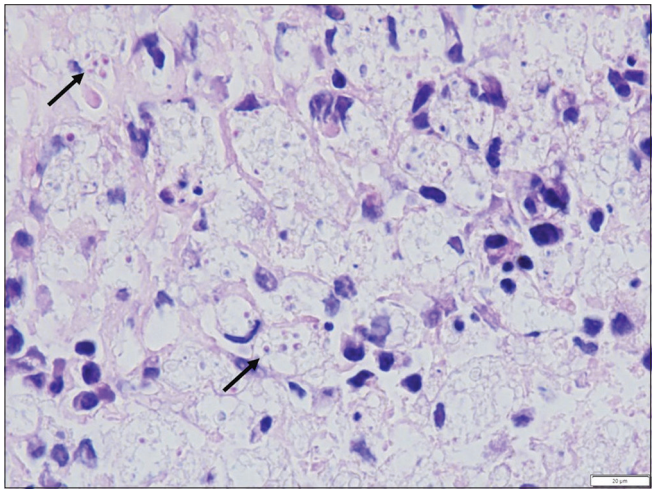

Figure 1: Microphotographs of lymph node biopsy showing macrophages with numerous intracellular yeast forms containing basophilic crescent-shaped nuclei with peri-cellular halo (H and E, ×1000)

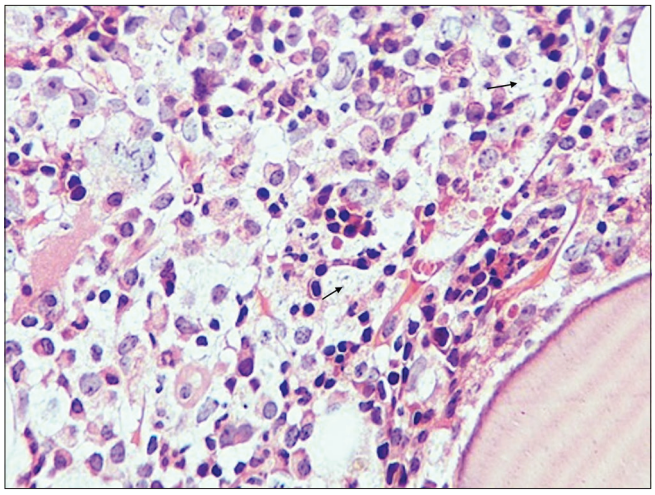

Figure 3: Microphotographs from bone marrow biopsy sections showing scattered histiocytes with intra-cytoplasmic pale-staining yeast forms of histoplasma (black arrows) (H and E, ×40)

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a state of hyperstimulation characterized by an uncontrolled and

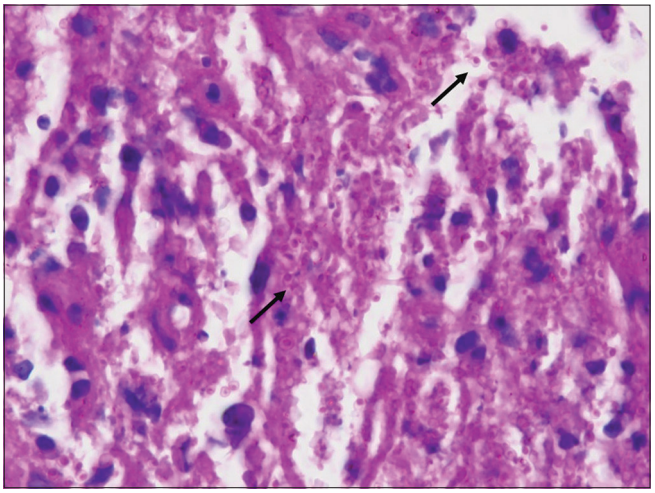

Figure 2: Microphotographs of lymph node biopsy showing yeast forms of histoplasmosis; better appreciated on PAS stain (PAS stain, ×1000). PAS: Periodic acid-Schiff

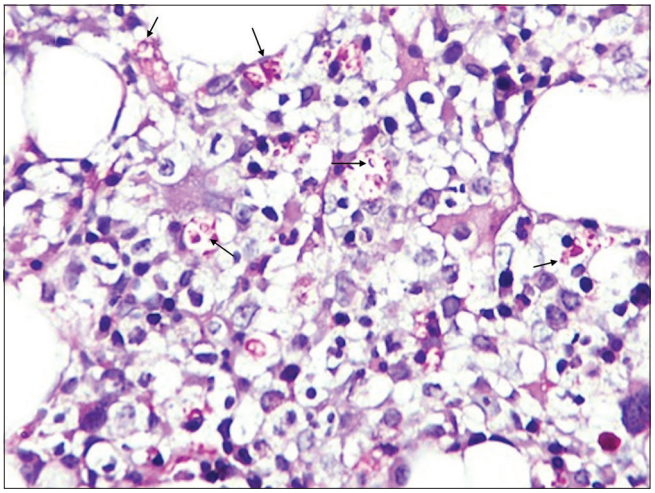

Figure 4: PAS positive yeast forms of histoplasma (black arrows) (PAS, ×40). PAS: Periodic acid-Schiff

ineffective immune response due to activation of NK-cells and macrophages with overproduction of cytokines and hemophagocytosis.[1] It can have an acute worsening course leading on to multiorgan dysfunction or slow course like pyrexia of unknown origin. It is divided into primary or familial, predominantly in children and secondary type seen in adults. In adults, most of cases are due secondary triggers like infections, malignancies, and autoimmune diseases.[1-3] Diagnosis of HLH is based on HLH-2004 criteria that is presence of either one of two: (1) identification of known genetic mutation or (2) 5 out of 8 criteria like fever, cytopenia of >2 cell lines, splenomegaly, hypertriglyceridemia or hypofibrinogenemia, ferritin >500 µg/L, soluble CD4 >2400 U/mL, hemophagocytosis on bone marrow, spleen or lymph node, and absent or low NK cell activity.[2] H-score is also used for diagnosis of HLH, with a range of score from 90 to 250 with a probability of HLH from <1 to >99% based on score.[4]

Hemophagocytic lymphohistiocytosis is an underdiagnosed and under recognized entity in patients with HIV. HLH has been described to occur in setting of acute HIV infection itself, immune reconstitution inflammatory syndrome, and opportunistic infections.[5] Predominant opportunistic infections leading on to HLH are EBV, HHV-8, CMV, HSV, disseminated histoplasmosis, toxoplasmosis, and mycobacterium tuberculosis.[6] Disseminated histoplasmosis is the one of the leading causes of HLH in HIV patients.[6,7] Major challenge lies in overlap of many clinical and laboratory findings (like fever, cytopenias, jaundice, hepatosplenomegaly, and raised ferritin levels) between AIDS and HLH as well as those with opportunistic infections.[8] Majority of these patients are young males, in advanced AIDS staging and very low CD4 counts.[6,8] Delay in diagnosis can be life-threatening in the absence of availability of serological tests like urine for histoplasma Ag and nucleic acid amplification test. Isolation of histoplasma from tissue like in our cases is gold standard for diagnosis. Treatment of disseminated histoplasmosis consists of liposomal amphotericin B (3.0 mg/kg daily) for 1–2 weeks, followed by oral itraconazole 200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months.[9] However, in case of nonresponders like in our case with HLH, immunosuppression with steroids or intravenous immunoglobulin may be required.[7] There are no data to support best-defined protocols for treatment and immunosuppression in HLH associated with disseminated histoplasmosis. Mortality has been reported to be around 30%–45% in various studies.[6-8] Our case highlights few points like HLH can have slow course like pyrexia of unknown origin and failure of response to primary therapy in HLH will require second like treatment like steroids and intravenous immunoglobulin.

Conclusion

HLH is an underdiagnosed condition in HIV patients. Opportunistic infections like disseminated histoplasmosis should be suspected in these patients. Early treatment with antifungals leads to better outcomes and however some patients will require immunosuppression in case of no response to primary therapy.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (http://www. equator-network. org/) guidelines, notably the CARE guideline, during the conduct of this report.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images related to histopathological specimen and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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