Case Report

Hemophagocytic Lymphohistiocytosis Secondary to Disseminated Histoplasmosis: A Case Report

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Abstract

Histoplasma capsulatum is a dimorphic fungus that can cause localized or disseminated infection. Disseminated histoplasmosis often presents with nonspecific features such as fever, hepatosplenomegaly, and pancytopenia, which may mimic haematological disorders, including leukaemia or aplastic anaemia. Timely recognition is crucial for favourable outcomes. We describe the case of a 67 year old woman who presented with progressive breathlessness, fever, and generalized weakness. Clinical examination revealed pallor and hepatosplenomegaly. What initially resembled pyrexia of unknown origin was diagnosed as hemophagocytic lymphohistiocytosis secondary to disseminated histoplasmosis, an extremely rare clinical entity. HLH is a rare immune dysregulation syndrome characterized by uncontrolled activation of macrophages and lymphocytes, leading to a severe inflammatory response and high mortality if untreated. The patient received antifungal therapy with liposomal amphotericin B followed by oral itraconazole, along with supportive care, resulting in significant clinical and haematological improvement. This case highlights the importance of maintaining a high index of suspicion for HLH in patients with unexplained fever and cytopenias, particularly in endemic regions, as early diagnosis and prompt therapy are vital for survival.

Keywords: Hemophagocytic lymphohistiocytosis, Histoplasmosis, Immunosuppression, pancytopenia.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening immune dysregulatory syndrome characterized by severe systemic inflammation. It may be primary due to genetic mutations or secondary to triggers such as infection. According to the 2004 revision of the diagnostic criteria for HLH, a patient must meet at least 5 of 8 criteria to be diagnosed with HLH. These criteria include fever, splenomegaly, cytopenia affecting at least two lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent natural killer cell activity, hyperferritinemia, and high soluble IL-2 receptor levels. Histoplasmosis-associated HLH is a rare but recognized entity. Patients commonly present with fever, weight loss, transaminitis, hypoalbuminemia, and cytopenias, and diagnosis is supported by Histoplasma serologies, urine antigen testing, and fungal blood cultures. We present a case of recurrent fever ultimately diagnosed as HLH secondary to disseminated histoplasmosis.

Case Description

A 67-year-old female presented with complaints of prolonged fever, shortness of breath, and fluctuating sensorium for 3 months with a history of hypertension and chronic kidney disease. Initially, a cerebrovascular accident was suspected. However, investigations revealed pancytopenia with elevated D-dimer, ferritin, and triglycerides, prompting further workup to identify the aetiology of pancytopenia and fever [Table 1]. Some of the investigations for presumed pyrexia of unknown origin were as follows
[Table 2]:

1. HRCT Chest: Suggestive of infective etiology with bilateral ground glass opacities and pleural effusion
2. MRI Brain: Normal study
3. Blood and Urine Cultures: Sterile (likely due to previous antibiotic exposure)
4. Bone Marrow Aspiration and Biopsy: Presence of multiple macrophages with multiple encapsulated yeast forms of Histoplasma Capsulatum along with engulfed neutrophils, platelets, and normoblasts.

Based on the above-mentioned reports, a working diagnosis of HLH secondary to disseminated histoplasmosis was formulated. The patient was started on intravenous liposomal Amphotericin B, followed by a maintenance regimen of oral itraconazole and supportive treatment, including blood transfusions to improve haemoglobin and platelet counts. The patient showed significant

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improvement in both clinical status and laboratory parameters and was subsequently discharged.

Table 1: Haematological parameters

Investigations	Day of admission	Day of discharge	Reference range
Hemoglobin	8.2 g/dl	12 g/dl	12-16 g/dl
Total Leucocyte Count	2.92/cumm	5.6/cumm	4000-11000/cumm
Total Platelet Count	68,000/cumm	2,50,000/cumm	150,000-450,000/cumm
AST/ALT	55/46 U/L	40/42 U/L	AST<40 U/L; ALT<40 U/L
T. Bilirubin	0.9 mg/dl	0.8 mg/dl	0.2-1.2 mg/dl
ALP	95.27 U/L	86 U/L	30-120 U/L
Urea/Creatinine	55.7/5.7 mg/dl	43/5 mg/dl	Creatinine: 0.6-1.2 mg/dl; Urea: 17-43 mg/dl
Na+/K+	132/4.4 mEq/l	136/4 mEq/l	Na+: 135-145 mmol/l; K+: 3.5-5 mmol/l
D-Dimer	1531 ng/ml	-	50-500 ng/ml
S. Ferritin	3000 ng/ml	-	11-307 ng/ml
S. Procalcitonin	1.17 ng/ml	-	0.25-0.5 ng/ml
S.LDH	186 U/L	-	140-280 U/L
S. Triglycerides	227.74 mg/dl		<150 mg/dl
HIV-1&2, HBsAg and Anti-HCV (Card Test)	Non-Reactive		

Table 2: Radiological, Microbiological and Bone Marrow Investigations

Investigation	Findings
HRCT CHEST	Suggestive of infective etiology with bilateral ground glass opacities and pleural effusion and partial lung collapse
MRI BRAIN	Normal Study
BLOOD AND URINE CULTURES	STERILE
SPUTUM EXAMINATION	No Growth Seen
BONE MARROW BIOPSY AND ASPIRATION	Presence of multiple macrophages with multiple encapsulated yeast forms of Histoplasma Capsulatum along with engulfed neutrophils, platelets and normoblasts
HISTOPLASMA SEROLOGIES AND URINE ANTIGENS	Not done due to financial constraints

Discussion

Histoplasmosis-associated HLH is rare but likely underdiagnosed due to its nonspecific clinical and laboratory presentation. Diagnosis is particularly challenging, as common features of HLH—including fever, cytopenias, splenomegaly, and elevated ferritin—are frequently observed in patients with disseminated histoplasmosis, as illustrated in our case.

Histoplasma capsulatum is an environmental dimorphic fungus and the causative agent of histoplasmosis, a disease with worldwide distribution and endemicity in North and Latin America and in several regions of Asia, including India and Southeast Asia. Infection typically occurs through inhalation of fungal spores from contaminated soil, with the lungs serving as the primary site of infection.[1] In disseminated histoplasmosis, infected macrophages result in the recruitment of more macrophages, causing further infection and histiocytosis. This predominantly affects the reticuloendothelial system, resulting in lymphadenopathy, splenomegaly, and bone marrow infiltration, as well as interstitial pneumonitis due to respiratory involvement. In immunocompromised individuals, the organism may disseminate beyond the lungs, leading to progressive disseminated histoplasmosis (PDH), a severe and potentially fatal condition if not promptly recognized and treated.[2]

This patient developed secondary hemophagocytic lymphohistiocytosis (HLH) triggered by disseminated histoplasmosis. Unlike primary HLH, which is characterized by inherited defects in natural killer cell and cytotoxic T-lymphocyte function, secondary HLH results from an exaggerated immune response to an underlying trigger, such as an infection.[3] Enhanced antigen presentation and toll-like receptor activation resulted in uncontrolled macrophage activation and excessive cytokine release. Subsequent overproduction of proinflammatory cytokines drives a cytokine storm with impaired immune downregulation, ultimately resulting in end-organ damage and metabolic derangements.[4]

Although HIV infection remains the most commonly reported immunodeficiency associated with HLH, an increasing number of cases have been described in non–HIV-infected patients. This case underscores the importance of recognizing disseminated histoplasmosis as a potential trigger of HLH in non–HIV-infected immunocompromised hosts.[5] This case is an example of the same, highlighting the need for heightened clinical suspicion and early diagnostic evaluation.

This case report describes HLH secondary to disseminated histoplasmosis and underscores the rarity of this association. It also underlines the importance of early recognition, as prompt initiation of appropriate therapy is critical to improving patient outcomes.

Conclusion

This case highlights the need for heightened clinical awareness of hemophagocytic lymphohistiocytosis (HLH) in patients presenting with prolonged fever and unexplained cytopenias. The overlap of clinical features between HLH and disseminated histoplasmosis makes diagnosis particularly challenging, yet timely recognition is critical to improving survival. Our patient's favourable outcome following antifungal therapy and supportive care underscores the importance of early suspicion, prompt diagnostic evaluation, and initiation of appropriate treatment. As HLH secondary to histoplasmosis remains rare

and underreported, further studies are warranted to establish standardized management strategies and better define prognostic indicators in adult patients with infection-associated HLH.

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Conflicts of interest
There are no conflicts of interest.

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