Journal of Pathology of Nepal (2024) Vol. **14**, 2180 -2182

Journal of
PATHOLOGY
of Nepal
www.acpnepal.com

Case Report

Histoplasmosis associated hemophagocytosis- a rare cause of pancytopenia in an immunocompetent patient

Mansimran Kaur[1], Menka Khanna[1], Karamjit Singh[1], Hitesh Marwaha[1]

[1]*Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research, Punjab, India*

Keywords:

Bone marrow;
Hemophagocytosis;
Histoplasmosis;
Pancytopenia

ABSTRACT

Pancytopenia as a result of hemophagocytosis in a middle-aged man presenting with high-grade fever of unknown etiology could be a rare consequence of Histoplasmosis infection.In the past, many cases of patients with human immunodeficiency virus infection contracting histoplasmosis-induced hemophagocytosis have been well documented, however, little data has been entered in the setting of HIV non-reactive status. Interestingly, we report a case of histoplasmosis in an immunocompetent male with the presence of yeast forms of H. capsulatum in the bone marrow smears. The patient was subsequently placed on Amphotericin B and corticosteroids but lost to the infectious disease. Cases like this, highlight the importance of taking into account the early decision for bone marrow sampling with careful attention to microscopic details as incidental pathologies may be elicited which could have significant effects on patient's prognosis.

Correspondence:
Dr. Mansimran Kaur
Junior Resident, Department of Pathology
Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India
ORCID ID: 0009-0007-8623-4869
Email id: mansimrankgrewal@gmail.com

Received : October 3, 2023; **Accepted :** March 23, 2024

Citation: Kaur M, Khana M, Singh K, Marhawa H. Histoplasmosis associated hemophagocytosis-a rare cause of pancytopenia in an immunocompetent patient. J Pathol Nep 2024;14(1): 2180-2. DOI:10.3126/jpn.v14i1.59030

INTRODUCTION

Histoplasmosis is a dimorphic fungus, pathogenic for humans and caused by two different varieties namely: *Histoplasma capsulatum var. capsulatum* and *H. capsulatum var. duboisii*.[1]The degree of severity in terms of life-threatening systemic disease is comparatively much higher in those with compromised cellular immunity than those with intact immune status.[2]Hemophagocytosis may be an important feature observed during marrow examination in cases of Histoplasmosis infection. Hemophagocytosis is the phenomenon of engulfment and phagocytosis of hemopoietic cells, neutrophils, erythrocytes, or cellular debris by

macrophages.[3]In India, the majority of histoplasmosis cases were reported from the eastern and north-eastern parts of the country, especially from Calcutta (West Bengal) and Assam.[1]

CASE REPORT

A 38-year-old chronic alcoholic with HIV seronegativity was admitted to the emergency department with the chief complaints of vomiting, fever, pain abdomen, loss of appetite, and altered sensorium for the last week. He also mentioned malaise and fatigue. There was no cough, shortness of breath, and any skin lesions. A physical examination of the patient revealed impaired general status, fever at 101^0 F, yellowish discoloration of the sclera, and hepatosplenomegaly. The laboratory and radiological investigations found pancytopenia (hemoglobin, 7.1g/dL; total leukocyte count, 2.5×10^9/L; and platelet count, 56×10^9/L), raised serum calcium levels, deranged serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). A careful examination of the peripheral blood smear showed no evidence of a haemoparasite. Blood culture examination tested negative for typhoid and tuberculosis. Rapid malarial tests for Plasmodium vivax and Plasmodium falciparum were also done and tested negative. In view of pancytopenia and unexplained pyrexia, bone marrow aspiration and biopsy were performed. The bone marrow aspirate smears were normocellular for age and showed mixed micronormoblastic and megaloblastoid erythropoiesis along with normal myelopoiesis and megakaryopoiesis. Furthermore, bone marrow examination spilled the evidence of hemophagocytosis with histiocytes showing presence of many intra-cytoplasmic and extra-cellular yeast forms of Histoplasma Capsulatum (fig. 1a and 1b). Grocott methenamine silver (GMS) and *Periodic acid–Schiff* (PAS) stain demonstrated capsule positivity of the H. Capsulatum. The patient initially responded to Amphotericin-B and Corticosteroids with improvement in the general condition of the patient with liver function tests and haematological parameters returning to the normal values. However, after 1 week of starting the medical therapy, the patient succumbed to death.

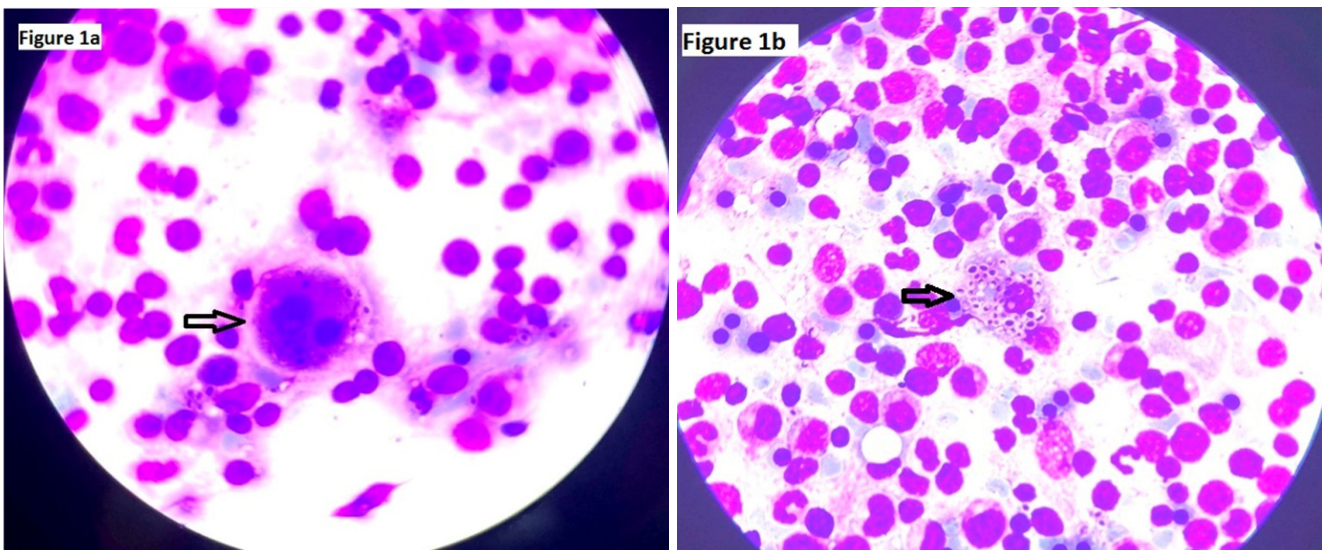

Figure 1a and 1b: *Bone marrow examination showing the phenomenon of hemophagocytosis along with the presence of intracellular and extra-cellular yeast forms of H. Capsulatum. (Giemsa stain, x1000)*

DISCUSSION

Disseminated histoplasmosis is a rare fungal infection with a spectrum of illness ranging from a chronic, intermittent course in immunocompetent persons to an acute and rapidly fatal infection that usually occurs in infants and severely immunosuppressed persons.[4,5] Symptoms include fever, malaise, anorexia, and weight loss. Hepatosplenomegaly and lymphadenopathy are also common findings.[6] Laboratory evaluation frequently reveals pancytopenia caused by bone marrow involvement and abnormal results on hepatic function tests, indicating that the disease has spread to the liver.[4,5,7]Markers of inflammation, including the erythrocyte sedimentation rate, C-reactive protein, and ferritin, are elevated, and hypercalcemia secondary to granulomatous inflammation has been described.[8]The most commonly used method for the demonstration of the parasite includes the examination of Giemsa or Leishman-stained smears of bone marrow aspirate. The yeast form of *H. Capsulatum* is often confused with *Leishmania donovani* amastigote forms (LD bodies). However, there is a clear space of capsule around the nucleus in the former, and the capsule stains positive with PAS stain and silver methanamine stain. Pancytopenia may be associated with histoplasmosis, particularly in patients showing hemophagocytosis.The term Hemophagocytic Lymphohistiocytosis (HLH) refers to the clinical syndrome marked by a hyper-inflammatory condition that is due to raised levels of circulating inflammatory cytokines produced by a highly stimulated but ineffective immune process, and

DOI : 10.3126/jpn.v14i1.59030

it is uniformly manifested by an abnormal proliferation of histiocytes throughout the reticuloendothelial system with the engulfment of hematopoietic cells (hemophagocytosis).[9] In our case, cytokine storm has been suggested as one of the reasons for the patient's death fate along with hypokalemia-induced arrhythmias and heart failure. Based on studies conducted by Brito-Zerónet al, reactive hemophagocytic syndrome categorically carries a high mortality.[10]Antifungal therapy is indicated in chronic or disseminated disease and severe, acute infection. Amphotericin B is the agent of choice in severe cases, however, patients must be monitored for nephrotoxicity.[11]

CONCLUSIONS

It may be concluded that clinicians need to be aware of the occurrence of the phenomenon of haemophagocytosis in patients with unexplained fever and pancytopenia in the setting of an infectious process. Bone marrow examination even with routine stains is a useful diagnostic test when cultures and serological tests are unavailable. In today's time also, a pathologist's role in amalgamating clinicopathological features to make a complete diagnosis is highly rated. Timely recognition of the triggering pathogen can alter the treatment and prognosis in these cases with immediate anti-fungal drugs and control of macrophage proliferation and activation, but potentially fatal if not recognized and treated promptly.

Conflict of Interest: None

REFERENCES

1. Antinori S. Histoplasma capsulatum: more widespread than previously thought. Am J Trop Med Hyg. 2014;90(6):982-3. Crossref
2. Mittal J, Ponce MG, Gendlina I, Nosanchuk JD. Histoplasma Capsulatum: Mechanisms for Pathogenesis. Curr Top Microbiol Immunol. 2019;422:157-91. Crossref
3. Chandra H, Chandra S, Sharma A. Histoplasmosis on bone marrow aspirate cytological examination associated with hemophagocytosis and pancytopenia in an AIDS patient. Korean J Hematol. 2012;47(1):77-9. Crossref
4. Gurney JW, Conces DJ. Pulmonary histoplasmosis. Radiology. 1996;199(2):297-306. Crossref
5. Wheat J. Histoplasmosis. Experience during outbreaks in Indianapolis and review of the literature. Medicine (Baltimore). 1997;76(5):339-54. Crossref
6. Pamnani R, Rajab JA, Githang'a J, Kasmani R. Disseminated histoplasmosis diagnosed on bone marrow aspirate cytology: report of four cases. East Afr Med J. 2009;86(12 Suppl):S102-5. Crossref
7. Conces DJ Jr. Endemic fungal pneumonia in immunocompromised patients. J Thorac Imaging. 1999;14(1):1-8. Crossref
8. Murray JJ, Heim CR. Hypercalcemia in disseminated histoplasmosis. Aggravation by vitamin D. Am J Med. 1985;78(5):881-4. Crossref
9. Usmani GN, Woda BA, Newburger PE. Advances in understanding the pathogenesis of HLH. Br J Haematol. 2013;161(5):609-22. Crossref
10. Brito-Zerón P, Kostov B, Moral-Moral Pet al. Prognostic Factors of Death in 151 Adults With Hemophagocytic Syndrome: Etiopathogenically Driven Analysis. Mayo Clin Proc Innov Qual Outcomes. 2018;2(3):267-76. Crossref
11. Kurowski R, Ostapchuk M. Overview of histoplasmosis. Am Fam Physician. 2002;66(12):2247-52. Website