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CASE REPORT

Diagnostic insights into disseminated histoplasmosis: a case report highlighting bone marrow analysis

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ABSTRACT

We present a case of a 43-year-old immunocompromised female patient diagnosed with disseminated histoplasmosis on bone marrow examination, at clinical laboratory of Kasturba Hospital, Manipal, Karnataka, India. The patient, presenting with symptoms like weight loss, appetite loss, and pancytopenia, underwent bone marrow aspiration and biopsy. The bone marrow studies revealed HIV-associated changes and the yeast form of *Histoplasma capsulatum*, confirming disseminated histoplasmosis. Bone marrow examination is highlighted as a diagnostic tool with significant sensitivity in such cases. The report stresses on the importance of awareness and early diagnosis of histoplasmosis in immunocompromised patients, given its potential lethality and the need for timely therapeutic intervention for better prognosis.

Keywords: Histoplasmosis; HIV infection; Opportunistic infection; Pancytopenia; Bone marrow examination

INTRODUCTION

Histoplasmosis, also known as Darling's disease after the American physician Samuel Taylor Darling who first described it, is a systemic fungal infection caused by the inhalation of *Histoplasma capsulatum var capsulatum* spores (1, 2). This dimorphic fungus, predominantly filamentous in nature, is often linked to opportunistic infections. While typically not affecting healthy individuals, it can be life-threatening if not diagnosed promptly, especially in those with compromised immune systems. It is particularly severe in HIV-infected patients with CD4+ counts below 75 cells/mm^3, where it poses a high risk of spreading throughout the body. In AIDS patients without appropriate treatment, the mortality rate may approach 100% (3).

The fungus is mainly found in soil contaminated with bird or bat droppings. In India, histoplasmosis is rare, with a few cases reported primarily in Eastern India (4). Diagnosing disseminated histoplasmosis is challenging in non-endemic areas due to its symptoms overlapping with diseases like tuberculosis, leishmaniasis, and certain systemic malignancies.

Histoplasmosis presents in three primary forms: acute pulmonary, chronic pulmonary, and progressive disseminated (5). While the acute and chronic pulmonary types may resolve without specific inter-

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vention, the progressive disseminated form is critical and requires prompt treatment with systemic antifungals (6). Relapses, occurring in 10-20% of immunocompetent patients and up to 80% in HIV-positive patients, necessitate continued treatment (7).

Diagnostic methods include complement fixation tests for anti-H and anti-M antibodies, urine tests for Histoplasma antigens, and serum antibodies detection using histoplasmin (HMIN), an antigenic extract from *Histoplasma capsulatum (H. capsulatum)* mycelial culture. Detection in endemic areas is highly sensitive through urine testing. Cultures from sputum, blood, and bone marrow on Sabouraud dextrose agar are the gold standard for diagnosis, with bone marrow cultures being particularly indicative in cases of disseminated histoplasmosis. However, these cultures require four to six weeks for growth and their effectiveness depends on the load of the disease.

CASE REPORT

Presenting illness. A 43-year-old female, working as a veterinarian and with no prior significant medical history, was hospitalized on 12th October, 2019, due to a two-month history of fever, cough, vomiting post-cough, weight loss, appetite loss, altered taste sensation, and diarrhoea. On examination, she showed signs of anaemia and oral thrush. Given her symptoms and geographic location, tuberculosis was initially considered.

The laboratory findings showed decrease in red blood cell counts, white blood cell counts and platelet counts (Table 1), leading to pancytopenia.

The patient was subjected to bone marrow aspiration and biopsy due to pancytopenia. The bone marrow aspirate revealed dyspoiesis in the myeloid series, reactive lymphocytes, and an increased number of plasma cells. Notably, there was a significant presence of macrophages engaging in haemophagocytosis and platelet phagocytosis. The biopsy indicated heightened myelopoiesis with a rise in precursor forms, an increase in lymphocytes and plasma cells, a few atypical lymphoid cells, and dyspoietic megakaryocytes. These findings pointed to the changes associated with HIV. She was started on anti-retroviral therapy (Fixed dose combination of Tenofovir 300mg, Emtricitabine 200 mg and Efavirenz 600mg) and was subsequently discharged.

Second admission. A month later, on November 6, the patient returned with ongoing fatigue. She showed no signs of bleeding, but her liver and spleen were palpable. Her haemoglobin had decreased to 5.5g/dl, necessitating a transfusion of one pint of packed red blood cells. Liver function tests were abnormal {Aspartate transaminase (AST)-139 IU/L, Alanine transaminase (ALT)- 85IU/L and Alkaline phosphatase (ALP)- 408 U/L}, indicating drug-induced hepatitis, leading to a temporary halt in anti-retroviral therapy. A strongly positive direct Coombs test led to a diagnosis of autoimmune haemolytic anaemia, for which she received treatment before being discharged.

Final admission. The patient was readmitted on December 12, with fever, oral lesions, persistent fatigue, and difficulty in walking. Tests for malaria and dengue were negative. She presented with hypotension and palpable hepatosplenomegaly. Blood tests

Table 1. Laboratory investigations

Haematological Investigations	
Erythrocyte sedimentation rate (ESR)	30 mm/hr
Red blood cell count	3.65 x 10^6 cells/uL
Haemoglobin level	7.3 g/dl
Packed cell volume	23.1%
White Blood Cell count	2.3 x 10^3 cells/uL
Platelet count	115 x 10^3 cells/uL
Microbiological Investigations	
Antibodies to HIV-1	Reactive
Other investigations	
CD4+ T cell count	47.16 cells/mm^3
Sputum Acid fast bacilli and Gene Xpert	Negative

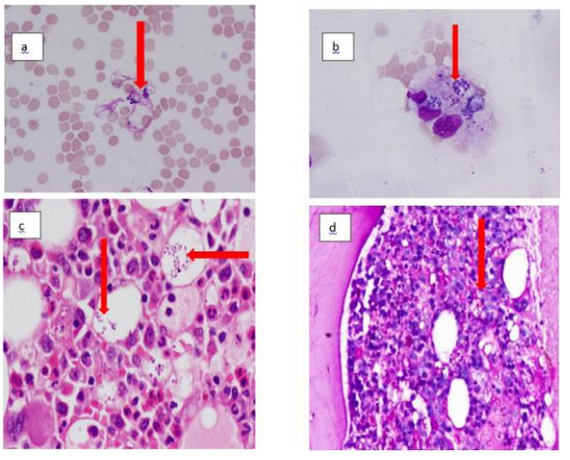

Fig. 1. (a) Leishman-stained peripheral smear showing *Histoplasma* (400×). (b) Numerous intracellular *Histoplasma* evident within histiocytes in Leishman-stained bone marrow aspirate (400×). (c) H&E and (d) PAS-stained stained bone marrow biopsy showing *Histoplasma* (400×).

showed continued pancytopenia, prompting another bone marrow examination. This revealed an increased number of macrophages with intracellular and extracellular yeast forms with a clear halo, indicative of *H. capsulatum*, as shown in Fig. 1 a-d. PAS staining confirmed the presence of the fungus, and mycology culture results were consistent with the bone marrow findings. Due to the complications of the underlying disease, she was transferred to the Intensive care unit. Unfortunately, she experienced cardiac arrest and passed away.

DISCUSSION

Histoplasma capsulatum, a dimorphic fungus, exists in both yeast and mycelial forms. Endemic areas, characterized by acidic and moist soil, are conducive to its mycelial growth, particularly in regions with bird and bat droppings. Typically, histoplasmosis infection is asymptomatic, becoming clinically significant primarily after substantial repeated exposure. In immunocompetent individuals, it often manifests as a self-limiting respiratory illness with symptoms like fever, malaise, cough, and chest discomfort. However, progressive disseminated histoplasmosis is rare in these individuals.

The systemic spread of *H. capsulatum* is more common among immunocompromised patients, affecting the reticuloendothelial system. The fungus appears as small oval structures with a clear halo around the nucleus (8, 9). Our patient, living in the hot and humid climate of Dakshin Kannada, a region favourable for *H. capsulatum* growth, and working as a veterinarian, faced increased exposure risks. Her HIV-positive status further compromised her immunity. She presented with non-specific symptoms like fever, hepatosplenomegaly, pancytopenia, and weight loss, complicating the diagnosis. The final diagnosis of disseminated histoplasmosis was made via bone marrow examination, confirmed later by culture.

Alterations in the Complete Blood Count (CBC), such as anaemia, leukopenia, or pancytopenia, are common in disseminated histoplasmosis, reflecting its systemic impact. Since CBC is a routine test that provides an overview of a patient's health, its alterations in histoplasmosis cases are significant for diagnosis and management (6). Culturing *H. capsulatum* is the definitive diagnostic approach, yet in our case, the diagnosis was initially identified through bone marrow studies.

Prior literature, including Mukherjee et al. and Subramanian et al. emphasizes the use of bone marrow examination in diagnosing histoplasmosis (5, 10). Similarly, Miranda et al. confirmed *H. capsulatum* presence in an oropharyngeal biopsy, and Wahab et al. diagnosed it in an adrenal mass through histomorphology (11, 12).

Histoplasmosis should be considered in the differential diagnosis for immunosuppressed patients presenting with unexplained fever, weight loss, hepatomegaly, and pulmonary symptoms. Bone marrow examination, particularly in HIV patients, is valuable for early diagnosis.

CONCLUSION

Histoplasmosis, primarily affecting immunosuppressed individuals, presents in various forms, including acute and chronic pulmonary as well as progressive disseminated types. Its potential lethality underscores the need for heightened clinical awareness, prompt diagnosis, and appropriate treatment to mitigate mortality risks. Bone marrow evaluation plays a crucial role in the early detection of disseminated histoplasmosis, leading to timely therapeutic interventions and improved patient outcome.

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