Disseminated Histoplasmosis with Reactive Haemophagocytosis Presenting as PUO in an Immunocompetent Host


Abstract
Disseminated histoplasmosis (DH) with reactive haemophagocytosis has been described in literature mainly in immunocompromised hosts. Only sporadic case reports exist in immunocompetent hosts. Here, we present a rare case of DH with reactive haemophagocytosis in an immunocompetent host presenting as PUO.

INTRODUCTION
Histoplasmosis, a fungal infection, has been reported from different parts of the world. Sporadic cases have been reported from India and other Southeast Asian countries in both immunocompetent and immunocompromised hosts. The clinical manifestations are variable – acute primary, chronic cavitatory and progressive disseminated. In an immunocompetent host, it usually leads to chronic disseminated disease. In Indian patients, skin and mucosa are the most commonly involved sites, with or without systemic involvement. Reactive haemophagocytic syndrome (RHPS) is a non-malignant syndrome characterized by an expansion of the monocyte-macrophage population and intense haemophagocytosis. It can occur de novo, but more often it occurs in the setting of another disorder, usually an infection or a malignancy. Here, we report case of disseminated histoplasmosis (DH) with reactive haemophagocytosis in bone marrow presenting as PUO in an immunocompetent host.

CASE REPORT
A nonalcoholic, nonsmoker 43 year old male, resident of Uttar Pradesh, manufacturer and seller of organic manure was admitted with complaints of fever for the last 3 months. Fever was low to moderate grade, not associated with chills and rigors. There was no history of cough, jaundice, urinary and bowel complaints. Examination revealed a febrile patient (101°F) with hepatomegaly (3 cm) and splenomegaly (7 cm). There was no lymphadenopathy. Respiratory, cardiovascular and nervous system examinations were essentially normal. Patient was investigated on lines of pyrexia of unknown origin (PUO). Haemogram revealed haemoglobin 9.2 g%, TLC 6200/cmm, platelets 1,80,000/cmm and ESR 32 mm/1st hour. Routine biochemistry and radiological investigations done for PUO were within normal limits. Mantoux test was negative and bacterial cultures did not reveal any growth. ELISA for HIV was negative on two separate occasions with normal CD4 counts. Giemsa stained bone marrow aspirate smears from sternum revealed a normocellular marrow, normal M:E ratio, normal trilineage hematopoiesis with increase in plasma cells and histiocytes. Numerous 2-4 µm oval to round bodies with eccentric to central nuclei and a perinuclear vacuole were identified within the histiocytes. These bodies were identified extracellularly also. Some of the histiocytes showed phagocytosed red blood cells and platelets (Fig. 1). A provisional diagnosis of histoplasmosis with reactive haemophagocytosis was made and trephine biopsy was performed. Biopsy revealed similar findings on H & E stain(Fig. 2). Special staining with silver methanamine and periodic acid Schiff stain confirmed the diagnosis.

Patient’s consent could not be obtained for any other invasive procedure such as liver biopsy. He was put on antifungal therapy (Tab Itraconazole 200 mg BD) and was continued for 6 months. Bone marrow culture collected later on was positive for H. capsulatum. Within 4 weeks of antifungal therapy, patient became afebrile and hepatosplenomegaly started regressing in size.

DISCUSSION
Disseminated histoplasmosis (DH) is a systemic illness which usually presents in a non-specific manner with persistent fever and constitutional symptoms. Differential diagnosis of histoplasmosis includes leishmaniasis, toxoplasmosis and other fungal infections like cryptococcosis, candidiasis and...
coccidioidomycosis. It is a disease of worldwide occurrence, endemic in great river valleys of American and African continents. In India, it is as yet a rare disease. Few case reports are available from Bengal, Maharashtra and other parts of the country.

Infection is usually acquired by inhalation of soil enriched with bird and bat droppings. Clinical manifestations are of three types—acute primary, chronic cavitatory and progressive disseminated. In an immunocompetent host, it usually leads to chronic disseminated disease. Signs and symptoms of DH are fever (most common), headache, weight loss, cough (in less than 50% of cases), hepatomegaly, splenomegaly, lymphadenopathy and jaundice.

The diagnosis of DH depends on demonstrating the organism in an extrapulmonary location in a patient with progressive illness either by culture of body fluids or infected tissue, or by microscopic examination of materials obtained from involved sites (liver, spleen, lymph node and bone marrow). The disadvantage of culture is the several week period required for growth and identification of H. capsulatum. A distinct advantage of the microscopy is the speed with which diagnosis can be made and appropriate treatment instituted. Confusion of H. capsulatum with another yeast is unlikely by histopathology as the 2-4 µm intracellular forms are diagnostic of histoplasmosis. Other investigations that can be utilized to diagnose histoplasmosis include serological tests to detect antigen in urine and serum by radioimmunoassay (RIA) that has a sensitivity of 92%. Detection of antibody titres in serum (more than 1:32) also helps make the diagnosis with a sensitivity of 71%.

Haemophagocytic syndrome, a clinicopathological entity characterised by inappropriate monocyte activation, has been described in association with a variety of bacterial, parasitic and fungal infections (tuberculosis, typhoid, brucellosis, malaria, leishmaniasis, histoplasmosis etc.) and malignancy (T-cell lymphoma, acute leukemia). The syndrome is characterised by fever (≥ 7 days, peak ≥ 38.5°C), splenomegaly (≥ 3 cm below costal margins), cytopenias (affecting ≥ 2 of three lineages) and morphological evidence of haemophagocytosis in bone marrow or lymph nodes or spleen. Some of the above findings may not apply to a secondary haemophagocytic state and there may be reactive haemophagocytosis only, without meeting all the criteria of the full blown syndrome. The few case reports of DH with haemophagocytosis have been described in literature mostly in immunocompromised patients.

In our case, patient presented with history of prolonged fever which was diagnosed as a case of DH with reactive haemophagocytosis by the bone marrow smears, bone marrow biopsy and cultures from bone marrow. This patient was successfully treated with antifungal therapy. Perhaps, this patient acquired infection during handling of the organic manure (a professional hazard).

In countries like India, where the prevalence of tuberculosis is high, clinical diagnosis of DH is often not suspected. Though majority of patients of DH are immunocompromised, the diagnosis should also be suspected in an immunocompetent host with PUO as highlighted in our case. Timely diagnosis and management of this serious but potentially reversible condition is essential as 100% mortality is seen in untreated patients.

**REFERENCES**