Chronic Disseminated Histoplasmosis Bone Marrow Involvement in an Immunocompetent Patient

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Abstract Histoplasmosis normally do not affect immunocompetent individuals. Prolonged exposure may cause *chronic disseminated histoplasmosis*. Elderly male patient presented with fever, hematuria and pain in right hypochondrium. He had pallor, fever and mild hepatosplenomegaly. Investigations revealed anemia and thrombocytopenia. Giemsa stained bone marrow aspirate showed yeast-like cells, suggestive of *Histoplasma capsulatum*. PAS stained bone marrow aspirate and biopsy confirmed the diagnosis.

Keywords Immunocompetent · Chronic disseminated histoplasmosis · Hepatosplenomegaly · Bone marrow

Introduction

Histoplasmosis is a disease of worldwide occurrence caused by dimorphic fungus *Histoplasma capsulatum*. In India, till now only sporadic cases are reported. Clinical manifestations of histoplasmosis are of three main types-acute primary, chronic cavitary and progressive disseminated [1].

Disseminated histoplasmosis is defined as a clinical condition where fungus is present in more than one location. Disseminated histoplasmosis is a less common manifestation

of the disease and mainly infects immunodeficient (transplanted or AIDS) patients, as well as the very young or very old. The severity of symptoms and histopathology reflect the degree of patient immunocompetence. The most common signs and symptoms are fever, shivering, indisposition, weight loss, hepatomegaly, splenomegaly, peripheral lymphadenopathy; ulceration of oropharyngeal mucosa (in 25–75% of cases); bone marrow alterations (anemia, leukopenia, thrombocytopenia), and electrolyte abnormalities [2].

Acute disseminated histoplasmosis is a systemic granulomatous disease and can be misdiagnosed as severe community-acquired pneumonia. Acute disseminated histoplasmosis is uncommon in immunocompetent individuals and, in most of these patients, evolution is satisfactory. The disease may be self limited or subclinical. In some cases, depending on length of exposure, delay in diagnosis, and host response, the evolution may be unfavourable [2].

Chronic progressive course is typical of disseminated histoplasmosis in non immunocompromised middle aged to older adults. This form of histoplasmosis is more common in men than women. A history of recent exposure often cannot be elicited, and overt defect in immune function have not been identified in these patients [3]. Hence, chronic PDH is seen almost exclusively in otherwise healthy adults. Low grade fever, malaise, and oropharyngeal ulcers are common. CXR may reveal patchy infiltrates in one or more lobes with associated lymphadenopathy [4]. We report the case of immunocompetent patient who presented with the disease, probably as a result of prolonged exposure and delayed diagnosis.

Case Report

A 50-year-old male patient was admitted in Fortis Hospital, Noida on 17/06/09 with complaints of high-grade fever,

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rigors and sweats of 1½ month duration. There was also associated hematuria and pain in right hypochondrium since 2 weeks.

On general examination, the positive findings were fever and pallor. A systemic examination revealed a soft abdomen with tender palpable liver (4 cm) and a non tender palpable spleen (5 cm). Contrast enhanced CT thorax done outside on 15/06/09 showed mildly thickened bronchovascular interstitium with nodular, alveolar faint opacities and haziness in lower lobes of the lungs. In view to clinical presentation and CECT findings a diagnosis of tuberculosis was highly suspected in Indian scenario. A differential diagnosis of malaria/leishmaniasis/ typhoid were also thought of due to presence of fever and hepatosplenomegaly.

Laboratory investigations revealed anemia and thrombocytopenia. Malarial antigen was negative, malarial parasite was not detected on peripheral smears (thick and thin). Rapid test for typhoid IgM antibodies and widal were found to be negative. Antibodies for HIV 1 and 2 were not detected.

Urine examination revealed presence of protein (++) and blood (+++). LFT showed decrease in albumin (1.8 g/dl) with mildly elevated liver enzyme levels—SGOT (AST)—63 U/l, SGPT (ALT)—52 U/l, ALP—219 U/l and LDH—235 U/l. Serum electrolytes showed mild decrease in sodium level—129 mEq/l.

Ziehl Nielsen stain done on sputum smear showed no acid fast bacilli. Aerobic and anaerobic culture yielded no growth. AFB culture was also found to be negative. IgG

and IgM antibodies for leishmania were not detected in serological tests. Fungal culture was not done.

Bone marrow aspirate stained by Giemsa showed oval globose yeast-like cells measuring 3–4 mm × 2–3 mm in size, suggestive of *H. capsulatum* in proximity to irregular clusters of epithelioid cells showing vague granuloma formation. However no giant cell (Langhans or foreign body) on current aspirate slides. PAS stain revealed these yeast-like cells as bright eosinophilic structures. Hematoxylin and eosin stained bone marrow biopsy slides showed few ill defined non caseating granulomas. PAS stain done on bone marrow biopsy slides showed yeast-like cells with bright eosinophilic nuclei and clear halo round them highly suggestive of *H. capsulatum* (Fig. 1).

Discussion

H. capsulatum is a dimorphic fungus that remains in a mycelial form at ambient temperatures and grows as yeast at body temperature in mammals. The soil in endemic areas provides an acidic damp environment with high organic content that is good for mycelial growth. Highly infectious soil is found near areas inhabited by bats and birds. Birds cannot be infected by the fungus and do not transmit the disease; however, bird excretions contaminate the soil, thereby enriching the growth medium for the mycelium. In contrast, bats can become infected, and they transmit

Fig. 1 **a** Giemsa stained smear showing histoplasma. **b** PAS stained smear showing histoplasma. **c** H&E stained bone marrow biopsy showing histoplasma. **d** PAS stained bone marrow biopsy showing histoplasma

the fungus through droppings. Contaminated soil can be potentially infectious for years [5]. The patient is resident in part of Meerut where bats are quite common. In this case they might have served as the potential source of infection.

Infection with histoplasma is asymptomatic in 95% of cases. In immunocompetent patients it usually manifests as self limited respiratory infection comprising of fever, malaise, cough and chest pain. Chest radiograph may show focal infiltrates and hilar or mediastinal lymphadenopathy [6]. Clinical manifestations appear with continued exposure to large inocula. The initial pulmonary infection may disseminate systemically, with hematogenous spread, and produce extrapulmonary manifestations. Hematogenous spread to regional lymph nodes may occur through the lymphatics or the liver and spleen. Progressive disseminated histoplasmosis is rare in adult hosts who are immunocompetent. Systemic spread usually occurs in patients with impaired cellular immunity and typically involves the CNS, liver, spleen, and rheumatologic, ocular, and hematologic systems [5].

Chronic progressive disseminated histoplasmosis is a term used to describe the slowly progressive and generally fatal infection due to *H. capsulatum* that occurs mostly in older adults who are not overtly immunosuppressed. These patients have no obvious immunosuppression, but their macrophages clearly cannot effectively kill *H. capsulatum*. It is thought that there is a specific defect in the cellular immune response to this specific organism. The time course of the infection in these patients is measured in months, and the disease is uniformly fatal if not treated. This is in contrast to the rapidly fatal acute form of dissemination that occurs in infants and immunosuppressed patients [7]. In our study the patient is 50 years old individual who is immunocompetent, yet showed significant hepatosplenomegaly with bone marrow involvement.

The case was diagnosed as chronic disseminated histoplasmosis on the basis of histology and involvement of liver, spleen. Isolation of organisms by culture was not successful but histomorphological features were characteristic for diagnosis. Liam et al. [8] demonstrated the presence of fungal bodies in tongue biopsy and confirmed it as *H. capsulatum* by further staining with PAS/D and Gomori's methanamine silver stain. Williams et al. [9] made a diagnosis of Histoplasma in adrenal mass on histomorphology.

Subramanian et al. [10] in their article to study the clinical features and natural history of disseminated histoplasmosis in India stated that diagnosis of Histoplasmosis by histopathology and/or culture from following sites-bone marrow, adrenal gland, lymph node, etc., is confirmatory.

Progressive disseminated histoplasmosis occurs in 1 case per 2,000 cases in adults who are immunocompetent [5]. Hepatosplenomegaly was a significant mode of presentation in this case as well as in other reports by many Indian authors. Histoplasmosis is a common disease of worldwide occurrence and is endemic in great river valleys of American and African continents. It is as yet a rare disease in India. In India, Panja and Sen reported the first case of disseminated histoplasmosis. This was followed by many reports of histoplasmosis in residents of Bengal. Sporadic reports are from Maharashtra and other parts of the country [1].

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