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Case Report

Pathology Section

Disseminated Histoplasmosis in an Immunocompetent Patient Diagnosed on Bone Marrow Aspirate – A Rare Presentation from a Non-Endemic Area

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ABSTRACT

Histoplasmosis causing systemic fungal infection is commonly seen in endemic areas. In India, disease prevalence is more in eastern part of the country and there have been very few reports from southern part of India. The occurrence of disseminated histoplasmosis in immunocompetent individual is rare. We report a case of disseminated histoplasmosis in an immunocompetent individual with no underlying risk factors. The disease was not suspected clinically and was diagnosed by bone marrow aspirate incidentally.

Keywords: Bone marrow aspirate, *Histoplasma capsulatum*, Immunocompetent, Incidental finding

CASE REPORT

A 55-year-old female patient hailing from Kumbakonam (Tamilnadu) was admitted to our hospital with complaints of abdominal pain and progressive abdominal distention for the last one month. She also gave a history of fever on and off for the last three months. She had undergone aortic valve replacement for calcific aortic valve stenosis three years ago. There was no history of travel to the endemic areas. Her general physical examination revealed pallor and abdominal distention. There was no hepatosplenomegaly. Rest of the general and systemic examination was within normal limits. Her Laboratory results were as follows, Hemoglobin-10.4 gm/dl, Total leukocyte count - 12,500 cells/cumm; Polymorphs - 75%, Lymphocyte - 22%, Eosinophil -2%, Monocyte - 1%. Erythrocyte sedimentation rate - 22. Liver function test, renal function test and serum electrolytes were within normal limits. She was also tested for Malaria and Dengue antigen and was found negative.

Serological tests for Human Immunodeficiency Virus (HIV), Syphilis and Antinuclear Antibody (VDRL and ANA) were negative. Urine routine and culture reports were also normal. Her chest radiograph was within normal limits. Contrast Enhanced Computed Tomography (CECT) abdomen showed massive ascites and no organomegaly.

Her blood culture, both aerobic and anaerobic, showed no growth. Sputum for Acid Fast Bacilli (AFB) also tested negative. Stool for occult blood was found to be negative.

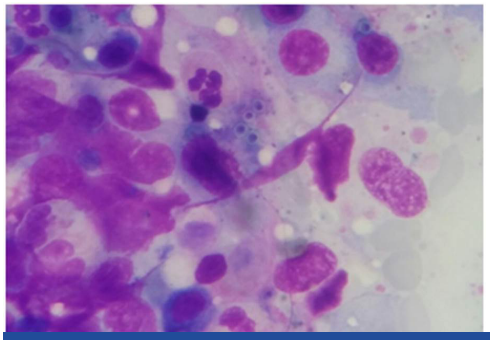
She underwent ascitic fluid aspiration twice and the sample was sent for cytology. It showed reactive mesothelial cells with few macrophages and no malignant cells/organisms. Biochemical evaluation of the fluid revealed exudative effusion.

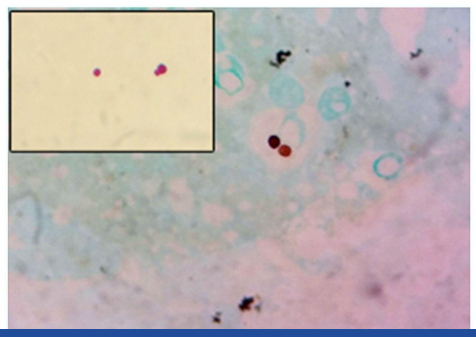
In view of her age and persisting ascites, a high index of suspicion for malignancy was noted and she underwent a bone marrow aspiration (BMA) and biopsy. BMA showed normocellular marrow with myeloid: erythroid ratio being 2:1. Erythroid series showed normoblastic maturation. Myeloid and megakaryocytic series were within normal limits. Plasma cells were increased in number (8%). In addition there were extracellular organisms measuring 3-4 microns in diameter, singly scattered as well as in groups [Table/Fig-1]. Some of them were showing narrow based budding and were surrounded by a clear space resembling *Histoplasma capsulatum*. This was confirmed by special stains (PAS, GMS & Perl's Stain) [Table/Fig-2,3]. Retrospectively we searched for the organisms in buffy coat and it also showed the presence of the organism. Patient was given injection Amphotericin B 0.7 mg for two weeks and tablet Itraconazole 200mg. Patient improved symptomatically and was advised to continue itraconazole for 12 months. Patient did not come for checkup after 6 months possibly due to relief of the symptoms.

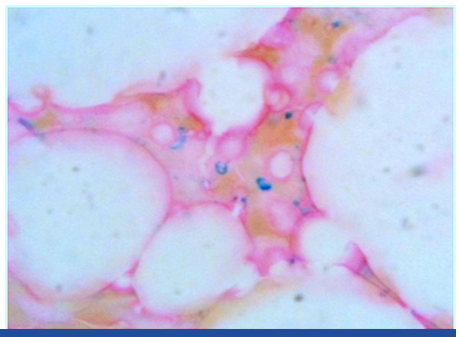
DISCUSSION

Histoplasmosis is endemic in the U.S (Ohio and Mississippi valley). It has also been reported worldwide in countries such as Africa, sub –Saharan Africa, South East Asia and India [1].

It is a dimorphic fungus i.e. it can exist as mycelial form (environment) and yeast form (inside the body). The transmission is through aerosols and not through person to person contact [1]. Our patient







[Table/Fig-1]: Bone marrow aspirate showing extracellular 3-4um sized organisms showing halo around these (MGG, 100X) **[Table/Fig-2]:** Encapsulated brown to black coloured structures (GMS, 100X); Inset shows PAS positive structures one of them showing narrow based budding (PAS, 100X) **[Table/Fig-3]:** These organisms showed positivity to perl's stain (Perls stain, 40X) (MGG-May Grunwald Giemsa, GMS- Gomori Methamine Silver, PAS- Periodic Schiff)

was exposed to bird droppings and this might be the probable cause for her to develop the disease. The clinical manifestations vary from asymptomatic to acute or chronic pulmonary histoplasmosis and disseminated histoplasmosis (spread to other organs and bone marrow). The progressive disseminated histoplasmosis usually affects the immunocompromised patients particularly those affected with HIV. It indicates impaired cell mediated immunity [1,2].

In India the first case of disseminated histoplasmosis (DH) was reported by Panja and Sen in 1954. There have been very few reports of disseminated histoplasmosis in immunocompetent individuals from non-endemic areas (South India) [3]. Histoplasmosis in immunocompetent individual is usually asymptomatic and sometimes manifest as minor illness such as cough, fever and chest pain. Chest radiograph shows hilar/mediastinal lymphadenopathy. These changes may mimic tuberculosis and may mislead the clinician [4,5]. Our patient had no pulmonary symptoms and had a normal chest x-ray which rules out pulmonary histoplasmosis. Acute pulmonary histoplasmosis is caused due to intense exposure to spores and can lead to fulminant acute form with shock and increased mortality.

The spores through the aerosol route are inhaled and deposited in the alveoli. The germinated spores are ingested by the pulmonary macrophages and spread to hilar and mediastinal lymph nodes and can spread to other organs via blood stream resulting in disseminated histoplasmosis [5].

The estimated incidence of disseminated histoplasmosis in healthy adults is approximately 1 per 2000 cases [6]. The study of disseminated histoplasmosis from South India was reported by Subramanian et al., in 2005 which included 19 patients in which only 4 patients were immunocompetent and only one was from southern region of India (Tamil nadu). BMA were done in 11 out of 19 patients and positive reports were seen only in 7 patients. In their study they stated that diagnosis of histoplasmosis by histopathology/ culture from bone marrow, adrenal, lymph node is confirmatory [1]. Deodhar et al., (2013) in their study on DH found that 6 patients out of 37 were immunocompetent. This study indicates the rise of presentation of DH in immunocompetent individual [7]. Histoplasmosis may cause ascites [5,8,9] due to peritonitis [8]. This might be the cause for developing ascites in our patient.

The diagnosis of organisms by means of culture testing takes 2 to 6 weeks and may not be an option in acute fulminant form which needs rapid interpretation and treatment and also in cases of self-limited disease demonstration of organism is difficult in culture [4].

Bone marrow examination has a 75% sensitivity in diagnosing fungal stains in HIV patients [3,10]. The differential diagnosis considered are *Leishmania, Candida, Cryptococcus, Blastomycosis and Pneumocystis carnii*. Amastigote form of leishmania may resemble the yeast form of histoplasmosis but can be differentiated by bar shaped kinetoplast and negative fungal stain. *Cryptococcus* and *pneumocystis carnii* are usually larger (2-20 microns) than histoplasmosis and present extracellularly. Blastomycosis has broad based budding when compared to histoplasmosis. The demonstration of histoplasmosis in Perl's Prussian blue iron stain was reported by Caldwell in 1982. *Candida* and *Cryptococcus* usually don't stain with Prussian blue stain [11]. Our case showed positive staining in Prussian blue stain and confirms the diagnosis.

Other diagnostic modalities include histoplasmin skin test which is due to delayed hyper sensitivity reaction, antigen detection from serum or urine and serum antibody assay by complement fixation and immune diffusion [12].

Amphotericin B is the drug of choice for this disease followed by azole groups. Lifelong treatment is required in HIV patients as relapse rates is more in these groups [1,13]. Our patient was given Inj. Amphotericin B 0.7 mg/kg for 2 weeks and she was continued with oral Iatraconazole 200mg thrice daily for 0ne year.

This case warrants discussion due to the nature of presentation i.e. from a non-endemic area (South India) in an immunocompetent individual who on presentation had no or minimal features of histoplasmosis which on contrary is common in most of the presented case series till date [14].

CONCLUSION

Awareness of histoplasmosis is important as this disease is still rare in non-endemic areas of India, has varying clinical course and its features overlap with those of other systemic illnesses including tuberculosis and malignancy. Presence of DH has to be borne in mind while treating spectrum of patients who are immunocompetent and additional testing methods have to be employed (BMA) to rule out histoplasmosis as early diagnosis and treatment is vital in this otherwise fatal condition.

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