Acta Biomed 2021; Vol. 92, Supplement 1: e2021134 DOI: 10.23750/abm.v92iS1.10213

Case report

Progressive Disseminated Histoplasmosis in an Immunocompetent Host: A Rare Presentation of an Uncommon Disease

Mehul Agarwal[1], Manohar Lal Gupta[2], Benhur Joel Shadrach[1], Neha Bharti[3]

[1]Department of Pulmonary Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India; [2]Department of Pulmonary Medicine, Santokba Durlabhji Memorial Hospital, Jaipur, India; [3]Department of Anaesthesia and Critical care, All India Institute of Medical Sciences (AIIMS), Jodhpur, India

Abstract. Disseminated Histoplasmosis, a systemic fungal infection caused by Histoplasma capsulatum is predominantly seen in immunocompromised cases. It is usually endemic, although sporadic cases have been reported. Following initial infection to the lungs, it disseminates to various organs by lymphatic and hematogenous routes. Clinical features are non-specific and depend on extent and severity of organ involvement. A Biopsy is required for diagnosis and timely intervention decreases morbidity and mortality. Our case report describes an atypical association of progressive disseminated Histoplasmosis with bone marrow involvement in an immunocompetent adult from a non-endemic region and alerts the clinicians to a rare yet life-threatening mycosis. (www.actabiomedica.it)

Key words: Disseminated Histoplasmosis, endemic, immunocompetent, biopsy

Introduction

Histoplasma capsulatum is a dimorphic fungus associated with systemic mycosis. Although prevalent in the West, it is uncommon and under-reported in other parts of the world. The first case of Histoplasmosis in India was reported in 1954. It is endemic along the Gangetic plains and in northern & north-eastern India, whereas other areas are considered relatively non-endemic for this mycosis (1). Presentation may vary from asymptomatic, acute, chronic pulmonary histoplasmosis, disseminated infection or mediastinal involvement. Disseminated histoplasmosis is the rarest form and usually occurs in extremes of age or in immunocompromised patients (2). Due to its rarity, non-specific clinical and radiological findings, variable progression and poor prognosis, the diagnosis and management is challenging. Here, we report a rare case of disseminated histoplasmosis in an immunocompetent middle-aged male who was managed successfully and a brief review of literature.

Case History

A 42-year-old non-Caucasian male, farmer, resident of Jaipur, Western India, never-smoker with no previous co-morbidities presented to the hospital with complaints of shortness of breath, low grade fever, loss of appetite, and significant weight loss (9kilograms) in the last 4 months. He also had a diffuse, non-radiating chest pain since last 25 days. Chest radiograph done 4 months back revealed bilateral nodular infiltrates (Figure 1A). He was started on anti-tubercular therapy (ATT) empirically at a local clinic with no relief and worsening of his symptoms. His vitals at

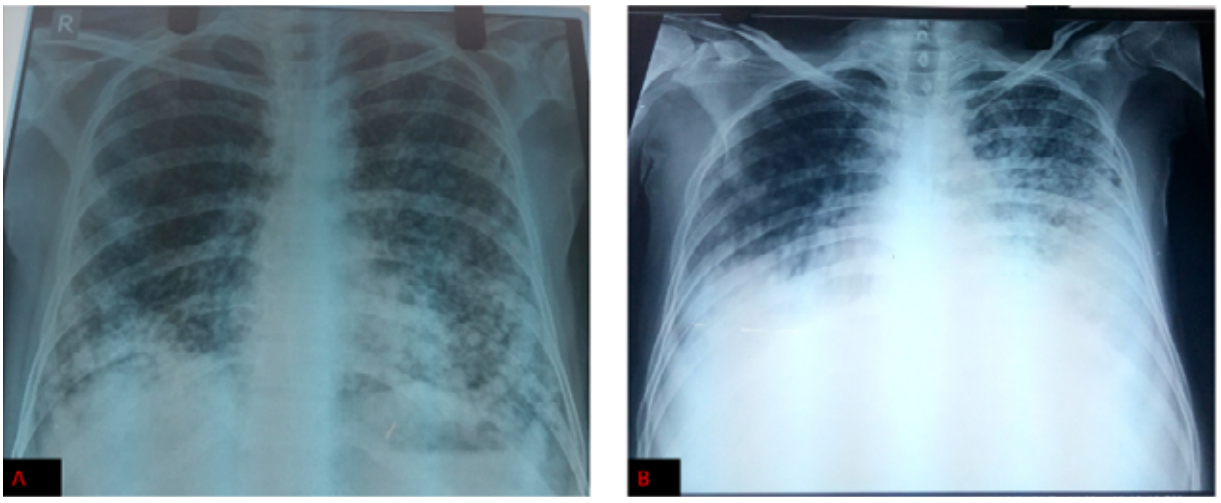

Figure 1. A) Chest radiograph showing near symmetrical fine nodular opacities, more in mid and lower lung zones. No obvious mediastinal, pleural, hilar or bony abnormality is present. B) Chest radiograph showing multiple small nodular opacities in bilateral lung fields. Lesions appear to have increased and are denser in comparison with previous radiograph

presentation were blood pressure 80/40 mmHg, pulse rate 144/minute, respiratory rate 28 breaths/minute, temperature 99.9°F, peripheral oxygen saturation (SpO2)- 83% on room air. On Respiratory system auscultation, bilateral coarse inspiratory crepitations were heard in mid and lower lung zones. ATT was stopped and he was started on supplemental oxygen therapy, intravenous broad-spectrum antibiotics, intravenous crystalloids and other supportive treatment. Chest radiograph revealed multiple small nodular opacities in bilateral lung fields, denser in comparison with the previous radiograph (Figure 1B). Initial laboratory investigations were Hemoglobin 10.9 gm/dl, total leukocyte count 2.78 x 10^3 µ/L with 83% neutrophils, 16% lymphocytes, platelets 97 thousand, serum transaminases were slightly elevated (Alanine transaminase = 111U, Aspartate transaminase = 64 U), total proteins 5.6 gm/dl, albumin 2.2 gm/dl, and normal renal function tests. Viral markers were non-reactive. Blood and urine cultures were sterile. His CD4 count was 670 cells/mm. There was no history of underlying immunosuppression or immunosuppressive therapy. High resolution computed tomography (HRCT) of the thorax disclosed bilateral nodules in random distribution (Figure 2). Patient did not consent for transbronchial lung biopsy, so Bronchoscopy and Bronchoalveolar lavage (BAL) were performed. BAL fluid microbiological analysis was negative for infection. Ultrasonography of the whole abdomen showed hepatosplenomegaly and mesenteric lymphadenopathy (2cm in short axis). US guided Fine needle aspiration (FNAC) of the node revealed Histoplasma Capsulatum (Figure 3A-B). Subsequently bone marrow biopsy and aspiration were performed that also yielded the same organism (Figure 4A-C). He was labelled as a case of progressive disseminated Histoplasmosis and initiated on injection Amphotericin-B deoxycholate 0.8 mg/kg/day i.v for 14 days followed tablet Itraconazole 200 mg thrice a day for first three days followed by 200mg twice daily. He exhibited dramatic response to antifungal therapy after which he was discharged and advised regular follow-up. Follow up at two, six, and nine months showed significant clinical and radiological improvement (Figure 5A-C).

Discussion

Histoplasmosis also known as Darling's disease, caused by the dimorphic fungi Histoplasma capsulatum is an endemic fungal infection commonly seen in Midwestern United States, Central and South America especially within Ohio and Mississippi river valleys. It occurs as mycelial form in soil contaminated with bird or bat droppings and grows as yeast in host tissues. Infection mostly occurs via inhalation of spores and is

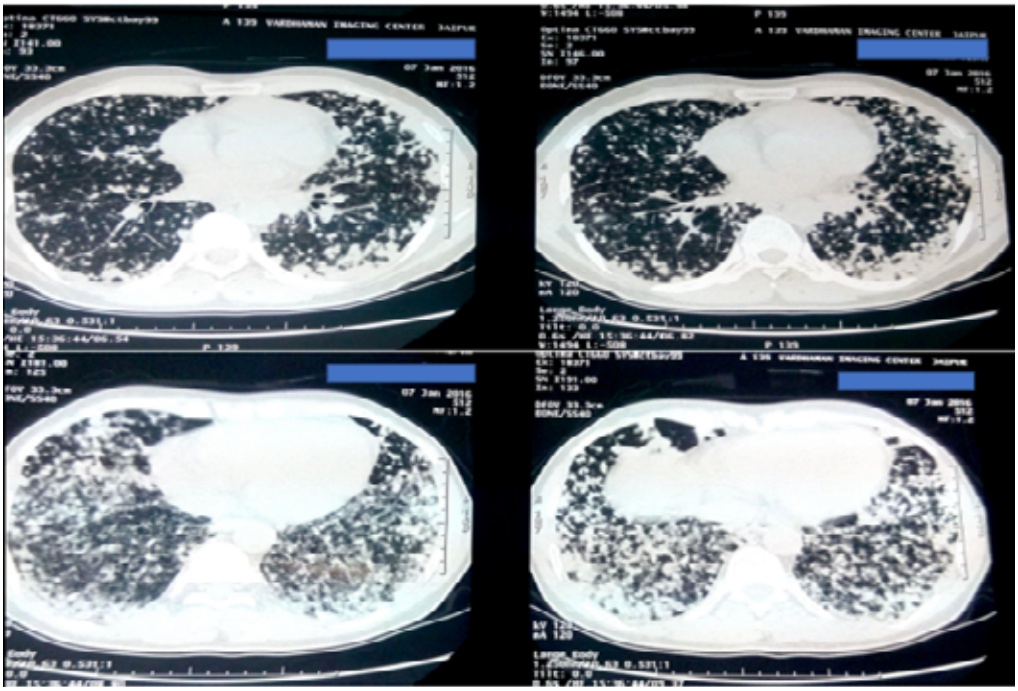

Figure 2. HRCT of the thorax axial section lung window showing random distribution of nodules with subpleural involvement and conglomeration of nodules.

most common in those involved in agricultural practices (3). It causes granulomatous inflammation and clinico-radiological profile closely mimics other granulomatous diseases especially pulmonary Tuberculosis which is the most prevalent granulomatous disease in this part of the world and sarcoidosis that is prevalent in the western world. Clinical features depend upon the type of presentation. Acute form usually occurs following heavy exposure leading to diffuse pulmonary infiltrates and respiratory insufficiency. Sub-acute

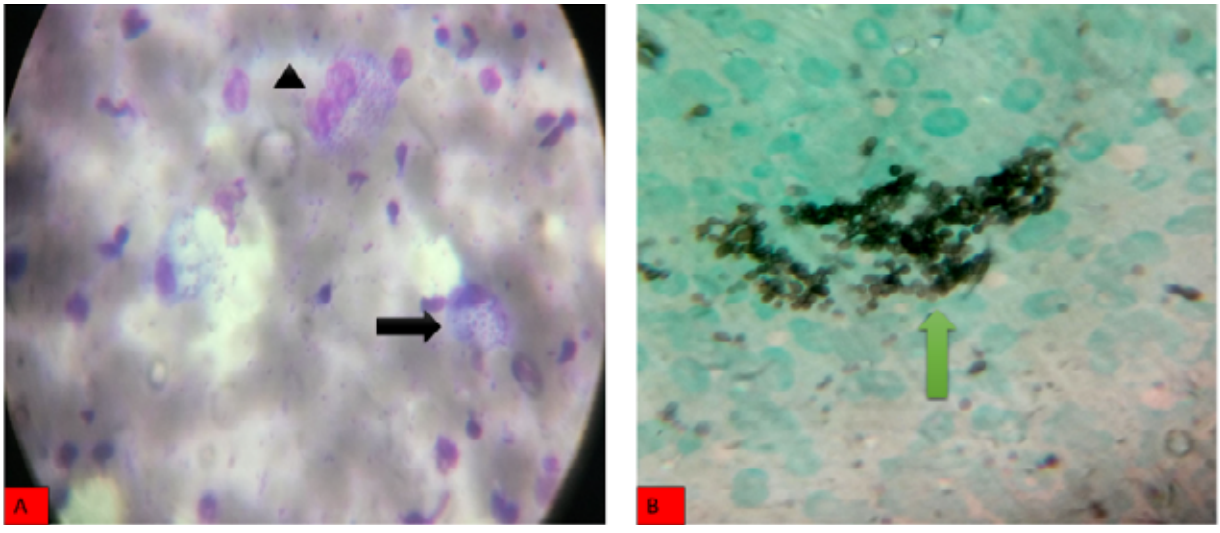

Figure 3. US guided FNAC from mesenteric Lymph node Giemsa stain (A) 1000x magnification showing large intra (arrow head) and extra cellular (arrow) yeast like cells. Methanamine silver stain (B) 1000x magnification showing histoplasma capsulatum (arrow)

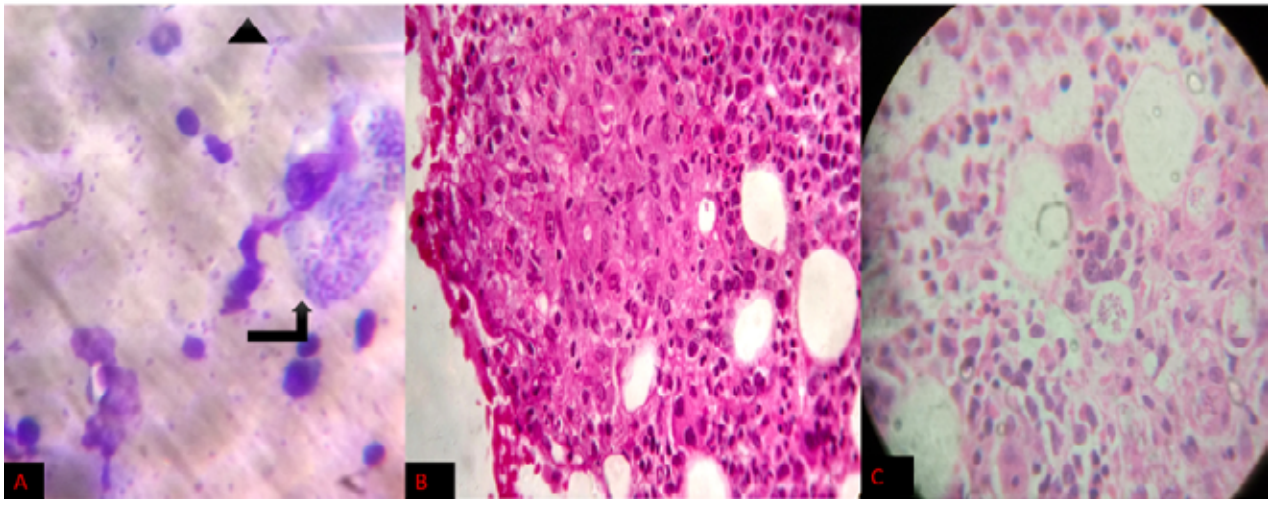

Figure 4. A) Bone marrow aspiration Giemsa stain 1000x magnification showing intra (arrow) and extracellular (arrow head) capsulated yeast form of histoplasma. B) Bone marrow biopsy sections H&E stain 400x magnification showing multiple epithelioid granulomas and C) revealing and intra and extracellular capsulated yeast form of histoplasma.

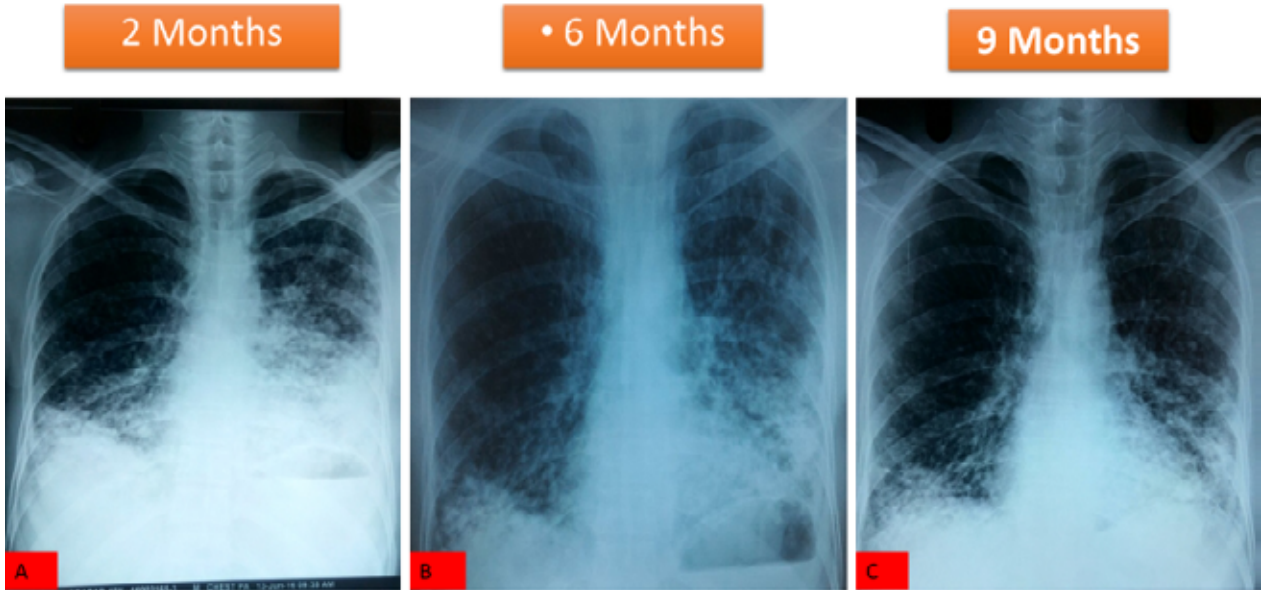

Figure 5. Serial radiographs taken at two, six, and nine months after initiation of antifungal therapy showing clearance of parenchymal infiltrates.

form is characterized by fever, cough, chest pain and patchy infiltrates. Mediastinal involvement is associated with compressive symptoms. Disseminated histoplasmosis or severe form of disease usually occurs in immunocompromised patients and is associated with constitutional symptoms such as fever, weight loss, loss of appetite, hepatosplenomegaly, lymphadenopathy, anemia, thrombocytopenia, and nodular infiltrates on chest imaging (4). Meninges, adrenals, oral mucosa, skin or gastro intestinal tract may also be involved. The commonest radiological finding includes nodular infiltrates. Differential diagnoses of nodular shadows on chest imaging include miliary tuberculosis, nocardiosis, blastomycosis, Cryptococcosis, sarcoidosis, tropical pulmonary eosinophilia, hypersensitivity pneumonitis, hematogenous metastasis, pneumoconiosis, and

amyloidosis (5). Definitive diagnosis is made by isolation of organism through biopsy and histopathology (HPE). Although our patient was immunocompetent and was from non-endemic region with no history of exposure or travel to an endemic region, he developed progressive disseminated histoplasmosis (PDH). Bone marrow specimen gives highest yield in disseminated histoplasmosis with hematological abnormalities (6). However, bone marrow involvement in PDH among immunocompetent has been rarely reported in the literature (7,8). Other tests available include cytopathology, antigen and antibody detection, skin prick tests and molecular tests with histoplasma-specific Polymerase chain reaction (PCR) assays, with varying sensitivity and specificity (9). Finally, management of severe Histoplasmosis includes intravenous injection Amphotericin-B in the first one-two weeks followed by tablet Itraconazole 200 mg twice daily for a total duration of 12 months. Dose of Lipid Amphotericin-B is 3-5 mg/kg/day while that of Amphotericin-B deoxycholate is 0.7 to 1 mg/kg/day (110). PDH has a variable clinical course and can be fatal with several studies reporting more than 80% mortality in untreated cases and excellent prognosis in those treated with appropriate therapy (11,12).

Conclusion

Progressive disseminated Histoplasmosis is an under-recognized entity in non-endemic regions and can occur even in immunocompetent individuals. Besides, it shares similar clinico-radiological and pathological profile with other chronic granulomatous diseases leading to misdiagnosis and delay in management. A high index of clinical suspicion is required especially when there is suboptimal response to initial treatment. Early recognition and definitive management with appropriate antifungal therapy confer better prognosis and survival.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Gupta A, Ghosh A, Singh G, Xess I. A twenty-first-century perspective of disseminated histoplasmosis in india: Literature review and retrospective analysis of published and unpublished cases at a tertiary care hospital in north India. Mycopathologia 2017;182:1077-93.
2. Pandey MK, Bajpai J, Kant S, Mishra P, Verma S. Histoplasmosis presenting as an intrathoracic mass. Lung India 2019;36:74-5.
3. Sareen R, Kapil M, Gupta GN, Govil A. Disseminated histoplasmosis in an immunocompetent individual presenting as oropharyngeal mass. Int J Oral Health Sci 2017;7 :48-52.
4. Gopalkrishnan R, Nambi PS, Ramasubramanian V, Ghafur KA. Histoplasmosis in India: Truly uncommon or uncommonly recognized?. J Assoc Physicians India 2012;60: 25-8.
5. Sharma BB. Miliary nodules on chest radiographs: A diagnostic dilemma. Lung India 2015;32:518-20.
6. Guimaraes AJ, Nosanchuk JD, Oliveria RMZ. Diagnosis of histoplasmosis. Braz J Microbiol 2006;37:1-13
7. Ling Q, Zhu W, Lu Q, Jin T, Ding S. Disseminated histoplasmosis in an immunocompetent patient from an endemic area: A case report. Medicine (Baltimore). 2018;97(29):e11486. doi:10.1097/MD.0000000000011486
8. Ganesan N, Sharma R, Phansalkar MD, Varghese R. Disseminated Histoplasmosis in an Immunocompetent Patient Diagnosed on Bone Marrow Aspirate - A Rare Presentation from a Non-Endemic Area. J Clin Diagn Res. 2015;9(12):ED07-ED8. doi:10.7860/JCDR/2015/14655.6894
9. Azar MM, Hage CA. Laboratory diagnostics for histoplasmosis. J Clin Microbiol 2017;55:1612-20.
10. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45:807–25.
11. Furcolow, M. L. 1963. Comparison of treated and untreated severe histoplasmosis. JAMA 183**:**121-127.
12. Reddy P, Gorelick DF, Brasher CA, Larsh H. Progressive disseminated histoplasmosis as seen in adults. Am J Med. 1970;48(5):629-636. doi:10.1016/0002-9343(70)90014-8

Correspondence:
Received: 13 July 2020
Accepted: 11 October 2020
Benhur Joel Shadrach
Department of Pulmonary Medicine,
All India Institute of Medical Sciences (AIIMS), Jodhpur
Phone number- +919655549072
Email id: benjoe6326@gmail.com