



Unusual Case Of Pneumonia In Indian Subcontinent “Darling’s Disease”

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Abstract

Histoplasma capsulatum is a dimorphic fungus found in many parts of the world in soil enriched with bird droppings of certain birds and bats. *Histoplasma capsulatum* is a dimorphic fungus. The mold or mycelia form exists as a mold in the soil where it absorbs nutrients from dead organic matter and produces infectious spores. When these spores are inhaled, they encounter the warm moist environment of the lungs. In the lung, the spores are ingested by macrophages and become yeasts. The disease may be asymptomatic or, in some cases, resemble tuberculosis. They undergo a transformation to the yeast or parasitic form.

Keywords: Dimorphic fungus, Sabouraud' agar, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Candida glabrata*, *Pneumocystis jirovecii*, *Coccidioides* spp

Introduction

The occurrence of histoplasmosis and its environmental sources of infection are reviewed. It covers the regional distribution of 388 cases of histoplasmosis reported since 1995 to till date. The highest number of cases occurred in West Bengal, followed by Uttar Pradesh, Delhi Union territory (UT), Rajasthan, Maharashtra, Haryana, and Bihar. (1) Histoplasmosis is an under-recognized disease in India and should be considered in the differential diagnosis of male patients with prolonged fever, adrenal enlargement, hepato-splenomegaly, oral ulcers and granulomatous disease on histopathology without response to ATT (2). Histoplasmosis affects children of any age. Being immunocompromised is a risk factor for severe and

disseminated disease. (3) Case of a 54-year-old male patient diagnosed with pulmonary histoplasmosis is reported, with the aim to increase the understanding of the disease characteristics and thereby facilitate the diagnosis and treatment of pulmonary histoplasmosis (4). Disseminated histoplasmosis is an AIDS-defining infection (and often referred to as progressive disseminated histoplasmosis), and co-infection with tuberculosis in AIDS patients presents further clinical challenges (5). Other immunocompromised states also pose a risk including solid organ transplantation (6). Recently collated older studies show the patchy distribution of Hcc in various areas around the world with case series in Brazil, South Africa, and in India (7,8).

Histoplasma capsulatum is an obligate intracellular pathogen that evades macrophage killing by entering the cell via CR3 and then altering the normal pathway of the phagosome maturation, in parallel to the strategies of intracellular bacteria such as *Mycobacterium tuberculosis* (9). A 48-year-old human immunodeficiency virus (HIV)-negative man with cervical and mediastinal lymphadenopathy, hepatosplenomegaly, adrenal mass, and bone marrow involvement was treated as disseminated tuberculosis without benefit. Progressive disseminated histoplasmosis was diagnosed from the fungus in smears from adrenal mass (10). In recent years, increased attention has been paid to endemic mycoses diagnosed outside of their established geographic ranges, including many with no known exposure to endemic regions. (11,12). The superficial intraoral lesions of histoplasmosis occurring concomitant to tuberculosis, in a 46-year-old man, an intraoral physical examination revealed diffuse, friable, vegetative areas on the right upper alveolar ridge, hard palate, and left inferior alveolar ridge (13).

Background

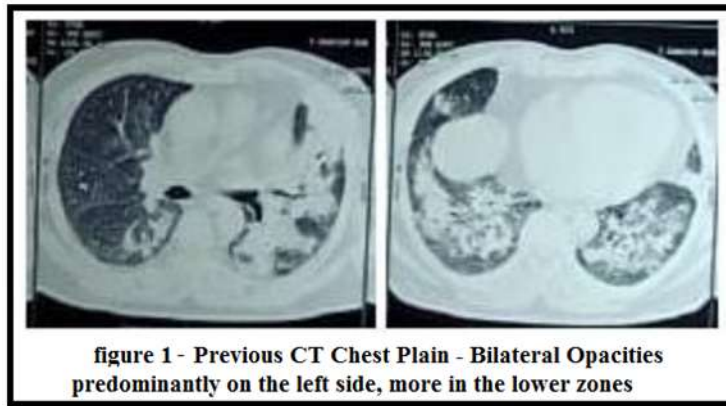
Histoplasma capsulatum is endemic to the Ohio, Missouri, and Mississippi River valleys in the United States. Internationally, the fungus is predominantly found in river valleys in North and Central America, eastern and southern Europe, and parts of Africa, eastern Asia, and Australia. *Histoplasma capsulatum* causes histoplasmosis. It is a systemic disease, mostly of the reticulo-endothelial system, manifesting itself in the bonemarrow, lungs, liver, and the spleen. In fact, hepatosplenomegaly is the primary sign in children, while in adults, histoplasmosis more commonly appears as pulmonary disease. This is one of the most common fungal infections. The ecological niche of *H. capsulatum* is in blackbird roosts, chicken houses and bat guano. Typically, a patient will have spread chicken manure around his

garden and 3 weeks later will develop pulmonary infection. Histoplasmosis is a significant occupational disease in bat caves in Mexico when workers harvest the guano for fertilizer. In the endemic area the majority of patients who develop histoplasmosis (95%) are asymptomatic.

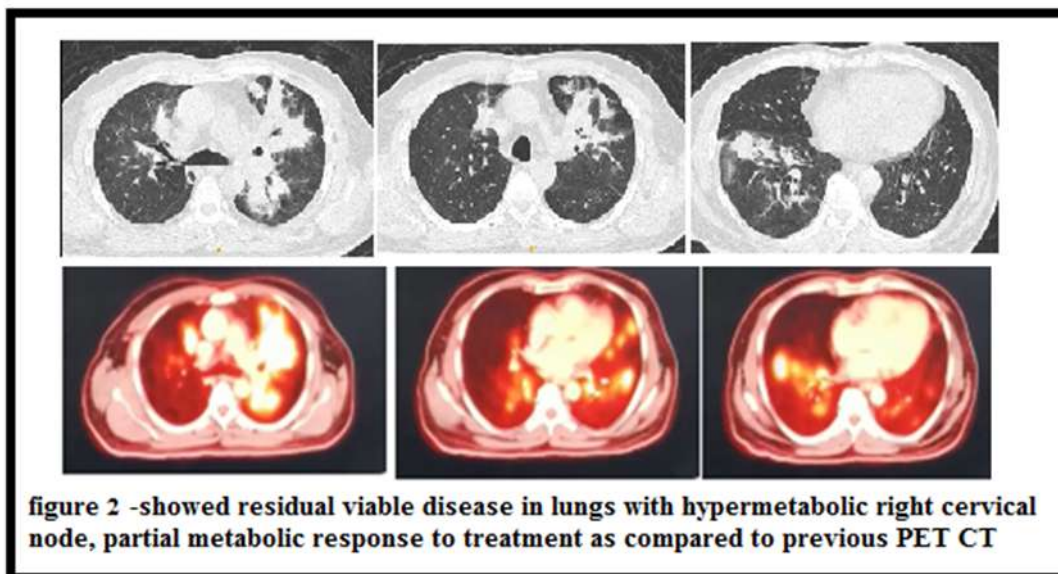
Case report

Unusual case of pneumonia in Indian subcontinent “darling’s disease” -

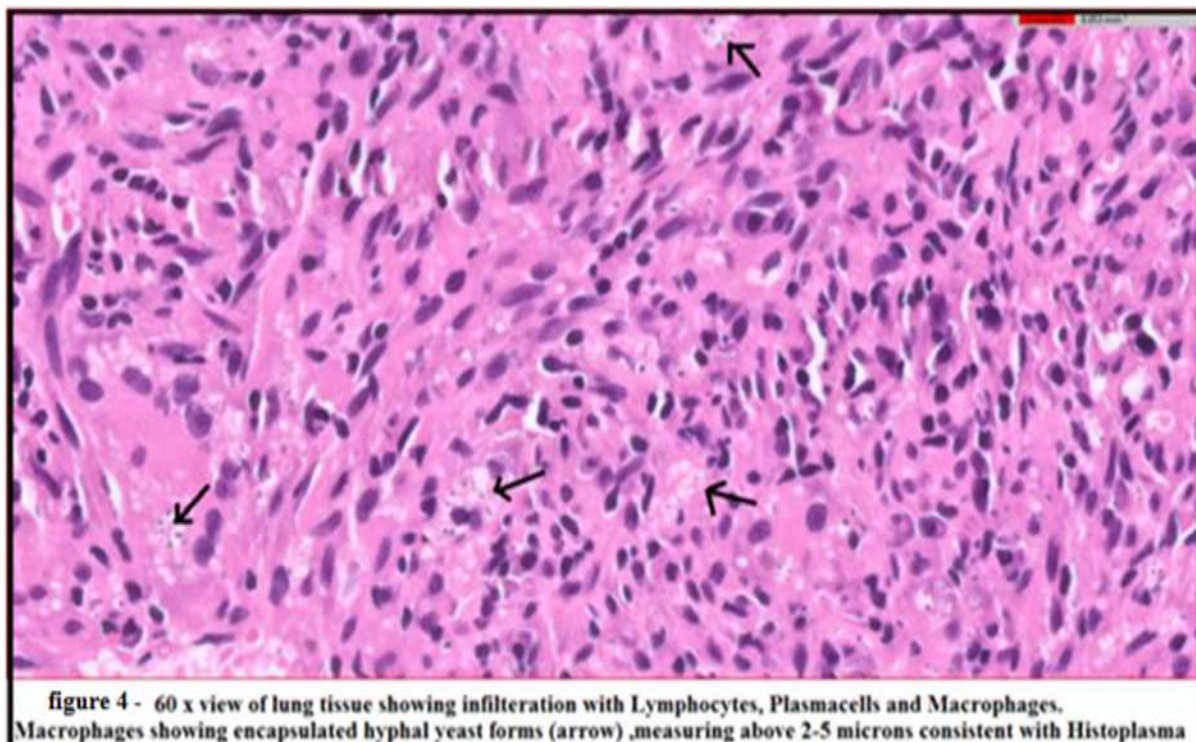
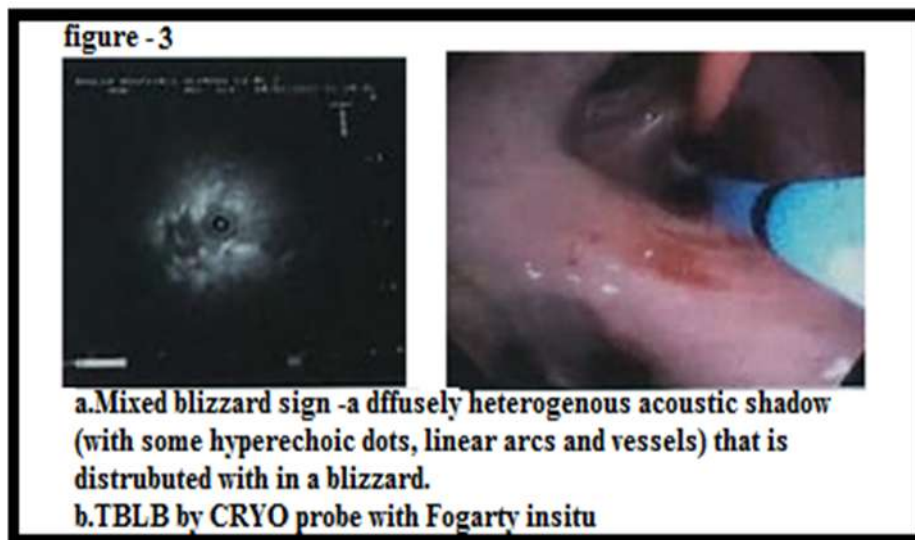
A 62 year elderly male patient known case of Hypertension from Jamshedpur presented with complaints of cough with occasional blood stained sputum and exceptional shortness of breath since one month. No history of skin and oral cavity lesions. There was history of significant weight loss (8kg in 2 months). Past history of Pulmonary TB in 1988. At the time of arrival vitals were stable with bronchial breath sounds on left side. Patient was admitted into outside hospital with Acute respiratory illness in October 2021 and was evaluated and treated as CAP with antibiotics. Despite of Treatment, he had worsening of symptoms and he was evaluated with further investigations- viral Screening was negative, RA factor was positive (15) and Rest of the autoimmune profile was negative. CT chest plain was performed which showed Bilateral parenchyma opacities (Left>Right) more in lower zone. PET CT was done which showed bilateral consolidations. As a part of further management ,Bronchoscopy was performed BAL collected from LLL and Conventional TBLB was performed .BAL examination showed budding yeast cells on fungal staining, Galcatomannan-2.36 , cytology was negative for malignancy and HPE showed acute inflammatory lesion. He was treated with Voriconazole for 9 days and treated with oral steroids in a tapering dose over 9 days.



Patient again had blood stained sputum, now came here for further management. PET CT was repeated, which showed residual viable disease in lungs with hyper metabolic right cervical node, partial metabolic response to treatment as compared to previous PET CT (figure 2).



In view of persistent symptoms, to evaluate etiology planned for Transbronchial lung biopsy using Cryo. Using Radial EBUS lesion localized to sub segments of superior and inferior segments of lingual. Under Fluro guidance 2 bits of cryo biopsy (figure 3) from superior segment and 2 bits from inferior segments of lingula were taken and sent for histopathology.



Histopathology of Cryo TBLB sample showed ill formed epidermoid granulomas with scattered multinucleated giant cells are seen and capsulated hyphal yeast forms, measuring above 2-5 microns are noted within the macrophages focally and Morphology is consistent with Histoplasma capsulatum (figure 4). After assessing for Disseminated Histoplasmosis, planned to give Amphotericin B for 14 days followed by Itraconazole 200mg thrice daily for 3 days followed by 200mg twice daily. After 2 weeks of assigned treatment,

Chest X ray repeated showed resolution of opacities and improvement in symptoms.

Discussion

Histoplasmosis is a systemic fungal infection caused by dimorphic fungus, *Histoplasma capsulatum* and presents most commonly as pulmonary, primary cutaneous and progressive disseminated (PDH) forms, the latter being more common in immunocompromised patients such as those with HIV infection. It was first described by Samuel Taylor Darling in 1906 in the viscera and bone

marrow of a patient suspected to have died from tuberculosis thus the name Histoplasmosis in humans has two clinical entities: Histoplasmosiscapsulati caused by *H. capsulatum* var. *capsulatum*, endemic in Eastern United States and Latin America and Histoplasmosisduboisii caused by *H. capsulatum* var. *duboisii*, prevalent in Africa and South East Asia. Infection is acquired by inhalation of infectious microconidia during activities like cleaning of chicken coops, visiting bat-infested caves, excavation, demolition of old buildings, and cutting of dead trees which lead to disruption of soil containing the organism and aerosolization of microconidia.

Histopathology remains an important diagnostic modality despite low sensitivity as a positive result permits initiation of specific antifungal therapy. Other pathogens that should be considered while making the histopathological diagnosis of histoplasmosis include *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Candidaglabrata*, *Pneumocystis jirovecii*, *Coccidioides* spp., *Talaromycesmarneffeii*, *Leishmania* spp., *Trypanosomacruzi*, and *Toxoplasma gondi*. Treatment of histoplasmosis includes an induction phase to achieve clinical remission and a maintenance phase to prevent relapse. These cases highlight the importance of high index of clinical suspicion regarding a differential diagnosis of histoplasmosis to prevent misdiagnosis and initiate early antifungal therapy and also merit discussion so as to create awareness among clinicians regarding this disease as its unusual in immunocompetent individuals.

Conclusion

Histoplasma capsulatum, a ground fungus, can infect humans, normally in endemic areas; the resulting disease can be asymptomatic or it can have a benign development, but in rare cases it can develop into a serious clinical condition and can even be fatal. Its most characteristic initial location is in the lungs, resembling tuberculosis, often accompanied by mediastinitis and an exuberant fibrotic response. *Histoplasma capsulatum*, a ground fungus, can infect humans, normally in endemic areas; the resulting disease can be asymptomatic or it can have a benign development, but in rare cases it can develop into a serious clinical condition and can even be fatal. Its most characteristic initial location is in the lungs,

resembling tuberculosis, often accompanied by mediastinitis and an exuberant fibrotic response.(14) Due to diverse and general, overall clinical presentation of histoplasmosis and the less in size index of mistrust, most of the infections are misdiagnosed or under reported. Endemic mycoses cause significant morbidity and mortality in immunocompetent and immunocompromised individuals worldwide and each has its own evolving regions of endemicity. Diagnosis is often missed or delayed, especially outside the areas of endemicity, due to a lack of awareness of the pathogen which is due at least in part to a scarcity of data on its geographic distribution (15) For suspicious cases based on medical history and imaging manifestations, bronchoscopy or CT-guided lung needle aspiration biopsy should be actively performed to facilitate the differential diagnosis of pulmonary infection. After the diagnosis is confirmed, effective and proper antifungal treatment should be timely delivered upon the individual situations, aiming to enhance the clinical efficacy.

Summary

Histoplasmosis is caused by *Histoplasma capsulatum* (Darling) which is yeast in its parasitic phase but in a filamentous fungus of soil at other times. The parasite in its yeast phase multiplies mainly in monocytes and macrophages and produces area of necrosis in which the parasites may abound. From these foci the blood stream may be invaded leading to metastatic lesions in liver, spleen and lymph nodes. Pulmonary histoplasmosis may produce pathological changes similar to those of tuberculosis. Diagnosis needs to be established through histopathology including fungal stains of granulomas, and/or cultures from appropriate specimens. Treatment with itraconazole leads to an excellent outcome in the majority of patients. It is, therefore, indicated that illustrations presenting by clinicians/scientists be more aware of the clinical manifestations, laboratory diagnosis, and risk aspects of histoplasmosis so that patients can be commence with medical therapy at the earliest and unnecessary complications can be avoided.

Take home points

1. In cases of Non resolving pneumonia , Suspect unusual causes like Tuberculosis, Vasculitis, organising pneumonia, Histoplasmosis, NTM,

Bronchio alveolar cell carcinoma, Pneumocystis, etc.,

2. Consider CRYO guided TBLB than conventional TBLB in such case as it has better yield and diagnostic ability.
3. Working as a well coordinated Multi disciplinary team involving Pulmonology, Radiology, Microbiology and Pathology in such cases facilitates early diagnosis and management.

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