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Fungal Infection Causing a Diagnostic Dilemma!

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Case Report

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ABSTRACT

Histoplasmosis is a fungal infection caused by Histoplasma capsulatum, which is distributed worldwide. Disseminated Histoplasmosis (DH) is one of its rare forms. Non-recognition of the true burden of Histoplasmosis in the Indian sub-continent is attributed to its possible misdiagnosis as Tuberculosis, malignancy or other diseases. We report a case of a young immunocompetent male who was diagnosed to have DH, later complicated by HLH. Timely diagnosis and treatment is the linchpin of management of DH, as it can prove fatal if left untreated. We present this case, taking it as our experience, to increase awareness regarding the presence of DH along with HLH, despite the immunocompetent status of our patient. Our case illustrates the challenges we posed during diagnosis; and how in TB endemic areas, pulmonary Histoplasmosis can be misdiagnosed.

Keywords: Histoplasmosis; Hemophagocytic lymphohistiocytosis (HLH); immunocompetent; Tuberculosis; adrenal enlargement; bone marrow biopsy; skin biopsy.

ABBREVIATIONS

DH : Disseminated Histoplasmosis
HLH : Hemophagocytic lymphohistiocytosis
TB : Tuberculosis
HRCT :High-Resolution Computed Tomography
mMRC : modified Medical Research Council
BUN : Blood Urea Nitrogen
ACE : Angiotensin Converting Enzyme
ACTH : Adrenocorticotrophic Hormone
IGRA : Interferon-Gamma Release Assays
PET-CT :Positron Emission Tomography – Computed Tomography
GGO : Ground Glass Opacity
VATS : Video-Assisted Thoracoscopic Surgery
AFB : Acid Fast Bacilli
MGIT : Mycobacteria Growth Indicator Tube
PCP : Pneumocystis carinii
LVEF : Left Ventricular Ejection Fraction
EPASP : Estimated Pulmonary Artery Systolic Pressure
IVIG : Intravenous Immune Globulin
AIDS : Acquired Immunodeficiency Syndrome

1. INTRODUCTION

American Histoplasmosis is a widely distributed disease, which is caused by Histoplasma

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capsulatum. The commonest environmental sources of H. capsulatum are soil around chicken houses, bat- infested caves and old buildings. Avian excreta contaminate the soil, thereby providing an enriched medium for growth of the fungus. DH is a rare form which is usually seen in immunocompromised individuals. It goes unrecognized in immunocompetent population, as it is usually expressed through nonspecific clinical manifestations such as prolonged fever, weight loss, oropharyngeal ulcers, hepatosplenomegaly, and/or lymphadenopathy [1]. Histoplasmosis usually affects the lungs, but involvement of other organs like bone marrow, liver, skin, adrenal etc are not uncommon. Lack of awareness and inadequate mycological diagnostic facilities are the contributory factors for its misdiagnosis as either Tuberculosis or Malignancy, in most cases [2]. Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulation syndrome characterized by persistent activation of the mononuclear phagocytic system, leading to proliferation and activation of histiocytes and lymphocytes that can cause an uncontrolled systemic hyperinflammatory response [3]. DH as a cause of haemophagocytic syndrome is infrequent and seen in those with immunocompromised status. However, HLH with histoplasmosis is extremely rare in an immunocompetent individual [4]. Diagnosis of Histoplasmosis can be established by either PCR based tests, Histopathology or culture reports. Timely management yields a good prognosis; but if left untreated, the disease spreads monstrously, which can even be fatal.

2. CASE REPORT

42 years aged male, resident of Varanasi, was the owner of a garment shop. He had no known comorbidities. He started complaining of intermittent low grade fever, cough with minimal white expectoration, and loss of appetite for a period of 1.5 months. HRCT Chest was done, which showed features suggestive of Non-Specific Interstitial Pneumonitis with tiny subcentimeter lymph nodes in pretracheal-retrocaval region. Complete workup for Tuberculosis was negative. Patient was referred to us in Mumbai, in view of persistent symptoms along with breathlessness - mMRCgrade 3 and loss of 20 kg weight in the past 2.5 months. On examination, he was vitally stable. On laboratory evaluation, abnormal findings included presence of raised S. Creatinine (1.95), raised S. ACE (>120), raised ACTH (101.2), low S.Cortisol. 2 D Echo showed Ejection Fraction of 45% with mild generalized left ventricular hypokinesia**.** However, Dobutamine Stress test was negative for ischemia with no regional wall motion abnormality seen. Unable to conclude towards a definitive diagnosis, a PET-CT scan was done, which showed enlarged adrenal glands with focalized areas of high grade activity(Fig. 1a) and diffuse low grade activity in the GGO's involving both the lung fields (Fig. 1b). Reactive pattern of uptake was seen in adjacent lymph nodes with no other organ involvement being noted. Patient was advised to undergo dual biopsy from adrenal gland and lung. After prolonged counseling, relatives agreed for lung biopsy and deferred for adrenal biopsy. Video-Assisted Thoracoscopic Surgery (VATS) of left lung was performed from 2 different lobes along with mediastinal lymph node biopsy. Histopathology of the lung biopsy showed granulomatous inflammation with interstitial fibrosis (Fig. 2a, 2b). Histopathology of mediastinal lymph node biopsy showed granulomatous lymphadenitis. All stains and cultures for TB, fungus, PCP and other bacteria were negative. Therefore, our provisional diagnosis was Sarcoidosis with or without Tuberculosis with primary adrenal insufficiency. Patient was initiated on anti Tubercular treatment along with oral Prednisolone (40mg/ day for 10 days, slowly tapering by 10mg per week) and returned back to Varanasi. Patient initially felt better, but later his complaints of fever, loss of appetite, further loss of 2kg weight and generalized weakness recurred. Patient travelled back to Mumbai. On examination, he had multiple ulcers and target shaped lesions over face and upper back. Since he had tachycardia and low BP, he was admitted to the ICU. HRCT chest was repeated which showed new acinar nodules in bilateral lower lobes. Laboratory investigations revealed bicytopenia (WBC -1300 and platelet-9000), deranged LFT, RFT, raised CRP (113), Procalcitonin (2.42), Lactate Dehydrogenase (1870), Ferritin (98,180) and Interleukin-6 (1474). Patient was empirically started on broad spectrum antibiotics, antiviral, antifungal (Amphotericin B) along with intravenous steroids. Anti-tubercular treatment was stopped. Bone Marrow and skin biopsies were performed. PCR test for Histoplasmosis was negative. Repeat 2D echo showed LVEF dropped to 25%. Bone marrow smear revealed cellular hemophagocytosis. Our working diagnosis was changed to a possible rare Granulomatous disease along with Drug induced Hepatitis, Adrenal insufficiency, Bicytopenia and HLH. Intravenous Immunoglobulin (IVIG) was started. Patient deteriorated hemodynamically,

and required mechanical ventilation along with high inotropic support. A day later, patient suddenly became unresponsive with cardiac asystole. All possible measures were taken, but unfortunately, could not revive our patient back. Next day, Histopathology of Bone Marrow and Skin biopsies showed the presence of Histoplasmosis (Fig.3a, 3b, 3c).

3. DISCUSSION

Histoplasma capsulatum is a dimorphic fungus which can exist as a mold in the environment and as yeast in tissues [1]. Histoplasmosis capsulati also known as American histoplasmosis or Darling's disease is caused by H. capsulatum var. capsulatum [1,2]. In India, most cases are observed from West Bengal, followed by Uttar Pradesh, Delhi Union territory (UT), Rajasthan, Maharashtra, Haryana, and Bihar [2]. Microconidia of the fungi are inhaled from soil, which settle in the alveolus and get ingested by the alveolar macrophages. The microconidia convert to the yeast form and replicate within the macrophages. They spread to the regional lymph nodes, and throughout the reticuloendothelial system. The infected macrophages induce cytokine response which

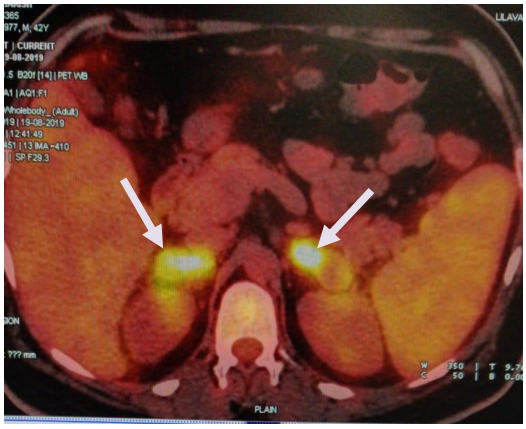

Fig. 1a.

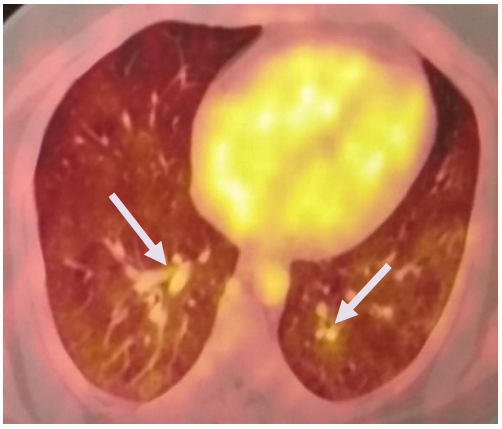

Fig. 1b.

Fig. 1a. Enlarged adrenal glands with focalized areas of high grade activity

Fig. 1b. Diffuse low grade activity in the GGO's involving both the lung fields

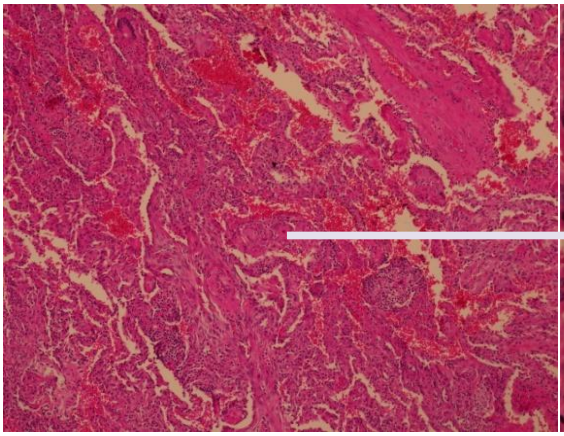

Fig. 2a.

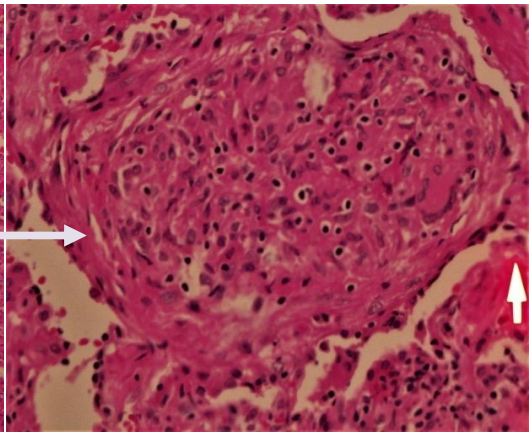

Fig. 2b.

Fig. 2a and 2b – Lung specimen showing granulomatous inflammation

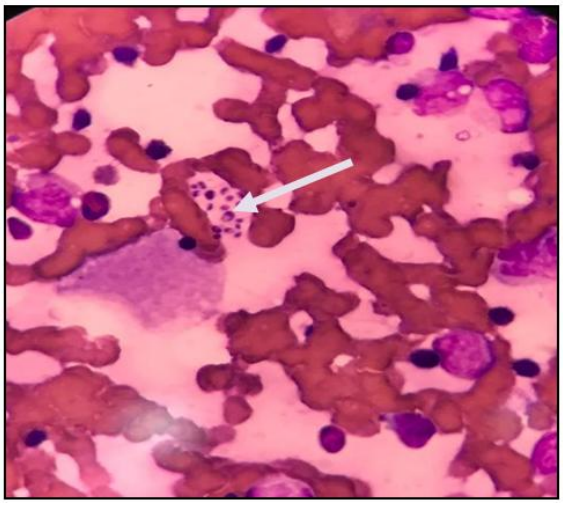

Fig. 3a.

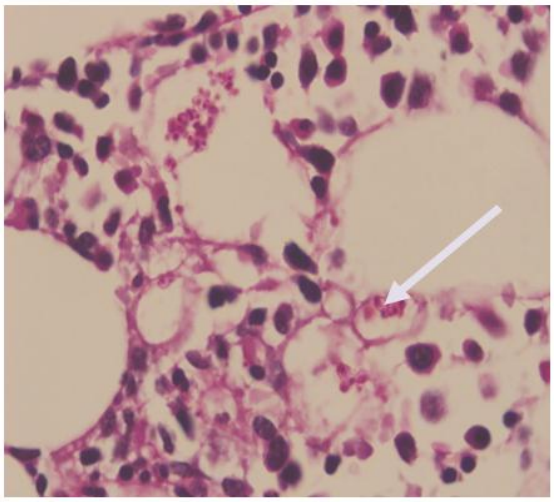

Fig. 3b.

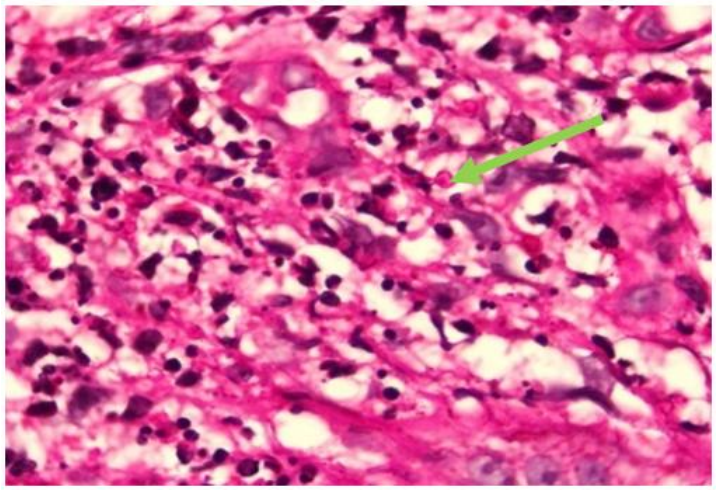

Fig. 3c.

Fig. 3a, 3b, 3c – Bone Marrow aspiration, Bone Marrow biopsy, Skin biopsy respectively showing presence of Histoplasmosis

attracts more macrophages and monocytes to fight the organism, and these coalesce to form a granuloma [5].

Histoplasmosis can clinically manifest as 3 main types - acute primary, chronic cavitary and progressive disseminated. DH is defined as a clinical condition where the fungus is present in more than one location. Among the forms of histoplasmosis, DH is the rarest and mostly found in immune-compromised individuals [5]. Progressive DH usually presents with hepatosplenomegaly, fever, anaemia, leucopoenia, weight loss, and generalized lymphadenopathy. Skin lesions in Histoplasmosis vary from polymorphic papules to plaques with or without crusts, pustules, nodules, mucosal ulcers, erosions, punched out ulcers, etc [6]. Males are more frequently affected than females, with male: female ratio of 4:1. Adrenal histoplasmosis is usually observed in transplant recipients, but does not seem to be uncommon amongst immunocompetent patients with disseminated histoplasmosis [2]. Typically, patients with adrenal histoplasmosis present with bilateral adrenal enlargement with normal

configuration. The presence of central necrosis and peripheral rim enhancements of the adrenals is seen in both tuberculosis and histoplasmosis. Hence histopathological examination is necessary, as it would exhibit typical microscopic features of H. capsulatum, although growth of fungus on specific culture medium, would give a definitive diagnosis [7].

Imaging in Histoplasmosis resembles features seen in Tuberculosis, exhibiting areas of consolidation with necrosis/cavitation and nodules. Enlarged hilar and mediastinal lymph nodes may be seen [8]. Polymerase Chain Reaction (PCR) diagnosis based on the amplification of fungal gene sequences is a powerful tool with high sensitivity and specificity for identifying invasive mycoses. Bone marrow biopsy for histopathology may be the most rapid method of establishing a definitive diagnosis of invasive infection [9].

Survival of histoplasmosis-induced HLH is very low and most are patients with AIDS [3]. In Histoplasmosis induced HLH, early antifungal therapy with a lipid formulation of Amphotericin B is critical although the initiation of immunosuppressive therapy should be individualized [10]. Clinical Practice Guidelines for the management of patients with histoplasmosis by the Infectious Diseases Society of America (2007) recommends Amphotericin B deoxycholate (1.0 mg/kg) daily for 4–6 weeks [11]. The mortality in untreated DH patients is as high as 80-100% but if treated with antifungal, this very high mortality rate is remarkably reduced to less than 25% [7].

4. CONCLUSION

Diagnosis of Disseminated histoplasmosis could pose a real challenge, but it should be considered as a differential diagnosis in patients exhibiting constitutional symptoms and hepatosplenomegaly. Despite the immune competent status, our patient developed Histoplasmosis as he hailed from an area which is endemic to Histoplasmosis. Although culture is gold standard for diagnosing disseminated histoplasmosis; biopsy with Histopathological examination from other involved sites like Bone marrow, skin and adrenal glands should be considered as they provide a good yield for early diagnosis. Timely diagnosis and early initiation of antifungal therapy is a must, as it grants a significant survival benefit and a better prognosis.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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