Experience of Varied Presentation of Chronic Progressive Disseminated Histoplasmosis in Immunocompetent Patients: A Diagnostic Conundrum

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Abstract
We report two cases of chronic progressive disseminated histoplasmosis with unusual and rare clinical picture in a patient with no underlying risk factor. One 50-year-old male, presented with hoarseness of voice, chronic cough, with a history of nonresponding anti-tubercular therapy, revealed mucocutaneous lesions on examination. Fungating vocal cord lesions were visualized on bronchoscopy, raised suspicion of carcinoma. The second case, a 22-year-old female, referred to hospital with suspected vasculitis, with complaints of “off and on” fever with decreased oral intake, arthralgia, who later developed generalized nodular skin eruptions. On investigation, human immunodeficiency virus test was found to be negative in both the cases. Histopathological findings of skin biopsy, adrenal and bone marrow aspirates raised suspicion, whereas fungal cultures confirmed *Histoplasma* infection. Although diagnosis was delayed, but both of them were successfully treated with amphotericin B.

Key Words: Antifungal, hemophagocytosis, *Histoplasma capsulatum*, immunocompetent, laryngeal lesion

Introduction
Histoplasmosis, a granulomatous fungal disease caused by a dimorphic intracellular fungus *Histoplasma capsulatum*. This saprophytic fungi present in soil rich with excreta of bats and birds. Hot and humid climate with high rainfall creates an ideal environment for sporulation. Macro- and micro-conidia are produced which infect human through aerosol inhalation and mainly affects reticuloendothelial systems. Only <1% of exposed persons develop clinical manifestations, mainly of three variants: Acute/chronic pulmonary, acute/chronic progressive disseminated, and rarely primary cutaneous histoplasmosis.[1] Clinically and microscopically it closely mimics tuberculosis, atypical localized pneumonia, *Penicilliosis marneffei*, leishmaniasis, syphilis, carcinoma. Cases of histoplasmosis have been reported from different parts of India since the first culture proven case was published from Calcutta 1954. Although misdiagnosis and underreporting are common due to the variable presentation, lack of clinical awareness, expertise, limited diagnostic laboratory.[2,3] Gangetic plains of West Bengal are an endemic pocket with high seroconversion rate as well as fungal isolation from the environment.[4] Patients having West Bengal domicile contributed maximum number in all case series reported form different Indian centers.[5]

Here, we report two atypical cases of disseminated histoplasmosis (DH), one with laryngeal involvement, and another with hemophagocytosis and diffuse cutaneous lesions.

Case Reports

**Case 1**
A 50-year-old male presented with complaints of hoarseness of voice since 18 months which was increasing in severity in last 2 weeks along with loss of appetite and weight loss. Six months back, he had dry cough with evening rise of temperature, diagnosed, and treated as pulmonary tuberculosis. He was in habit of chewing tobacco for 10 years but declared as nonsmoker, nonalcoholic, and never traveled overseas.

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Clinical examination revealed multiple large tender fungating lesions with necrosis over tongue and three small erythematous nontender papules over forehead, which were progressively increasing in size since last 1 month [Figure 1]. On basic laboratory investigations including complete blood count, liver and renal function tests, hepatitis B surface antigen, anti-hepatitis C virus, human immunodeficiency virus (HIV) 1/2 serology were within normal limits and nonreactive. However, chest X-ray showed unilateral healed foci of patchy lesion. Sputum microscopy was negative for acid-fast Bacilli, Mantoux test positive. Anti-tubercular regimen was started, but symptoms persisted. On laryngoscopy, inflamed endolaryngeal structures with multiple exophytic ulcerated nodules were documented on the right vocal cord, but biopsy could not be taken due to risk of bleeding. Punch biopsy was taken from skin and tongue lesions and sent for histopathological examination. It showed chronic granulomatous inflammation, dense infiltration of inflammatory cells and histiocytes into subepithelial fibrocollagenous tissue and profuse intracellular 2–4 µm cystic structures with prominent nuclei and perinuclear halo. No epitheloid granuloma or evidence of neoplastic pathology was found. With the suspicion of histoplasmosis, bone marrow biopsy was done. On abdominal ultrasonography, small opacity visualized on the left adrenal gland and caseous pus was aspirated from the abscess. Tissue from tongue, skin, sputum, bone marrow, and pus from adrenal was cultured on Sabouraud dextrose agar (SDA), brain heart infusion blood agar. After 2 weeks of incubation white floccose growth appeared from all the specimens, revealed hyaline, septate hyphae, and very characteristic tuberculate macroconidia, numerous pyriform microconidia on lactophenol cotton blue preparation, based on which the fungus provisionally was identified as Histoplasma spp.

He was successfully treated with amphotericin B 1 mg/kg body weight for 2 weeks then switched to itraconazole 200 mg, twice a day for 8 weeks and discharged on oral itraconazole. Complete resolution of the mucocutaneous lesions, return of normal vocal cord function, and dramatic improvement in voice quality was seen in follow-up. Repeat endoscopy showed regression of laryngeal lesions, which is indirect evidence of fungal etiology.

Case 2
A 22-year-old school girl from Midnapore district of West Bengal presented with intermittent low-grade fever, joint pain, and weight loss. She had suffered from minimal change glomerulonephropy, treated with oral glucocorticoid 5 years back. Suspecting it as a case of vasculitis, routine hematological, and biochemical investigations were done. Her antinuclear antibody profile and serology for malaria and dengue were negative, blood sugar, electrolytes, serum cortisol, urine and stool microscopy, chest X-ray were normal and splenomegaly found in abdomen ultrasonography. Biochemical tests showed markedly elevated serum triglyceride, lactate dehydrogenase, and ferritin levels. Hematological tests revealed pancytopenia with hemoglobin - 6.9 g%, total leucocyte count - 2800/cumm, and platelet count of 1 lac/cumm. This prompted us to do an HIV 1/2 serology and bone marrow biopsy for microscopy and culture. She was found nonreactive for HIV 1/2 and normal CD4 count, but bone marrow biopsy revealed hypocellular marrow with erythroid hyperplasia and histiocytes with phagocytosed red blood cells and platelets. A provisional diagnosis of hemophagocytic lymphohistiocytosis (HLH) was made as per criteria.[6] On day 5+, she developed high rise of temperature along with multiple erythematous, discrete, nontender, firm papules, nodules involving skin all over the body and face except scalp, palms, and soles [Figure 2]. No mucosal lesions found on examination. Punch biopsy of skin nodule was done for histopathological examinations and culture. Intracellular yeasts were present which took purple color in periodic acid–Schiff stain and black by Grocott’s methenamine silver stain [Figure 3]. The special staining differentiated fungi from other organisms with similar morphology. Then bone marrow slides were reviewed, and numerous oval refractile encapsulated yeasts were noted inside histiocytes as well as extracellularly [Figure 4]. Culture on SDA revealed growth of white mold with verrucous, tough, adherent colony with tuberculate macroconidia.

**Figure 1:** Fungating lesions over tongue (a) and multiple nodules on forehead (b) of Case 1

**Figure 2:** Nodular skin lesions disseminated whole body of Case 2
after 20 days of incubation that was reported as *Histoplasma* spp. [Figure 5].

The patient was managed with intravenous amphotericin B, at 1 mg/kg/day for 14 days followed by itraconazole.

Both the isolates were sent to the reference laboratory at Postgraduate Institute of Medical Education and Research, Chandigarh, India and confirmed as *H. capsulatum* by doing yeast conversion.

**Discussion**

Histoplasmosis is endemic mycoses, prevalent in Northeastern and Midwestern United States, also a frequent public health problem in the Asia-Pacific region, though ecologic niche for this infection remains elusive in this area due to limited epidemiological study. Chronic progressive DH is a rare and fatal variety which affects all systems, commonly seen among immunocompromised patients, particularly as an opportunistic infection among AIDS persons. A review showed DH is not uncommon in India in apparently immunocompetent individuals and presentations varied from epididymitis to bleeding manifestations.

Laryngeal histoplasmosis is very rare in Indian scenario and easily misdiagnosed as tuberculosis or carcinoma, especially when lesion biopsy is beyond scope, what happened in our first case. Correlation with other lesions, meticulous histopathological examination of all mucocutaneous lesions not responding to conventional treatment, search for systemic involvement and high index of suspicion are the key for diagnosis. As per reviews adrenal involvement occurs frequently among Indian immunocompetent cases, mostly not associated with adrenal insufficiency. It was also seen that adrenal gland biopsy material is more diagnostic than bone marrow aspiration for DH among immunocompetent patients. We could isolate fungus from bone marrow, skin of both the cases and also adrenal aspirate of the first case. In contrast to earlier studies who showed skin lesions, mucosal involvement, and pancytopenia are more common among immunocompromised patients, both of our cases presented with these features.

HLH is a rare syndrome characterized by a hyperstimulated, but the ineffective immune response and histoplasmosis is one of the triggering intracellular infections of secondary HLH in tropical countries. Eight cases of DH with HLH have been reported from India largely in immunosuppressed hosts, whereas only three patients were immunocompetent. Although histoplasmosis associated HLH is a rare entity, diagnosing only HLH by clinical and hematological criteria might miss the secondary cause of this syndrome which need specific antifungal treatment. The special fungal stain of bone marrow biopsy and culture isolation is required to differentiate histoplasmosis from leishmaniasis, an endemic disease with similar presentations in India.

As per guideline, amphotericin B for 1–2 weeks, followed by oral itraconazole for a total of at least 12 months is
recommended for DH. However, there is considerable controversy surrounding treatment of adult patients with secondary HLH, whether to use antifungal therapy alone or in combination with immunosuppressive agents.

**Conclusion**

Although high prevalence of histoplasmosis in West Bengal, very few number of cases actually diagnosed from local centers, due to lack of clinical suspicion and inadequate laboratory facilities. Our two cases with bizarre clinical picture will enlighten clinicians and make them aware about the presence of this endemic systemic fungal disease of Bengal, which will help to clinch the diagnosis early.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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**What is new?**

- Rare clinical presentations of histoplasmosis leads to diagnostic dilemma, specially in nonendemic countries
- We present two atypical cases of histoplasmosis, successfully diagnosed and treated.