Case Report

# A Rare Case Report-Idiopathic CD4 Lymphocytopenia Leading to Disseminated Histoplasmosis

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Histoplasmosis, a granulomatous mycosis caused by the intracellular dimorphic fungus *Histoplasma capsulatum*, has not been reported in Indian literature. The clinical spectrum of histoplasmosis varies from asymptomatic infections to disseminated histoplasmosis (PDH), depending on the intensity of the injury and the immunity of the exposed person. Infections most often occur in immunocompromised individuals, especially those with compromised immune systems such as HIV with low CD4+ lymphocytes, malignancies, or those who have received other immunosuppressive therapies. Keeping a high clinical suspicion regarding a differential diagnosis of histoplasmosis is required to prevent misdiagnosis, particularly in high-risk patients and initiate early antifungal therapy, which ameliorates the patient's prognosis. Here, we present a case report of a middle-aged diabetic man who presented in our institute as a referral case from a private hospital with complaints of anorexia, fatigue, low-grade fever and decreased urination for 2 months with subsequent weight loss. His bone marrow biopsy confirmed infiltration with *H. capsulatum*. Subsequent 6 week apart CD4 counts were less than 300/mm$^3$ without HIV-positive status or other acquired immunodeficiency, consistent with idiopathic cd4 lymphocytopenia. After a varied clinical course of intensive care stay, the patient was well treated with antifungal medications, showed remarkable improvement and was subsequently discharged in good condition.

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## Introduction

*Histoplasma capsulatum*, a thermally dimorphic fungus, is the etiologic agent of histoplasmosis. Mycelia—the naturally infectious form of *Histoplasma* have a characteristic appearance, with microconidial and macroconidial forms. Shortly after infecting the host, mycelia transform into the yeasts that are found inside macrophages and other phagocytes. The yeast forms are characteristically small (2–5 μm), with occasional narrow budding, Figure 1.[1-3] Activities associated with high-level exposure include excavation, cleaning of chicken coops, demolition and remodeling of old buildings, and cutting of dead trees. It is primarily a pulmonary disease but can progress to disseminated disease in immunocompromised patients.[3] In our patient's subsequent 6 weeks apart, CD4 counts were less than 300/mm$^3$ without HIV positive status or other acquired immunodeficiency, consistent with idiopathic CD4 lymphocytopenia,[4] which led to such dissemination, which was finally diagnosed only after bone marrow examination.

### *Case report*

A 45 year old male working at a grain house was referred from a private hospital where he was admitted in view of decreased appetite, generalized fatigue, low-grade fever and reduced urine output since the past 2 months, with co-morbidities type 2 diabetes mellitus and systemic HTN since 10 years, on regular medications. He was diagnosed with right-eye ischemic optic neuropathy 3 years back.

On general examination, the patient was found to be cachexia and febrile. The pulse was 104 per minute, Blood pressure was 100/70 mm of hg in right upper arm- supine position and the respiratory rate was 32 per minute with a tracheostomy tube in situ on SIMV mode of ventilation, Fio 2 to 70%. Pallor- present, no lymphadenopathy.

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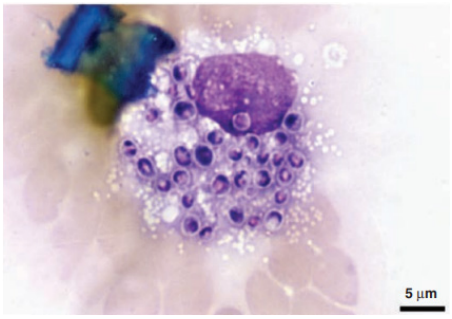


**Figure 1:** Intracellular yeasts of *H. capsulatum* within an alveolar macrophage

Systemic examination revealed- the liver was enlarged, firm, tender, and 6 cm below the right coastal margin. The spleen was also palpable, firm, nontender and 4 cm below the left coastal margin. Respiratory system -coarse crepitations in the bilateral interscapular and infrascapular region.

Routine investigations revealed anemia, thrombocytopenia, an increased alkaline phosphatase level, raised inflammatory markers and negative viral markers like HIV/Hbsag/HCV (Table 1).

Chest x-ray- suggestive of bilateral ground glass haziness with obscured right CP angle.

USG whole abdomen showed Mild to moderate hepatomegaly with moderate splenomegaly.

### *CECT chest*

- Diffuse B/L ground glass haziness with mild septal thickening.
- Right-sided mild pleural effusion.
- Few sub-centimeter-sized mediastinal lymph nodes.

### *CECT abdomen*

- Moderate hepatomegaly with marked splenomegaly and splenic infarct.
- Moderate ascites.
- Few enlarged lymph nodes along the celiac axis/ hepatic artery.

### *Bone marrow aspiration*

smear shows oval budding yeast-like parasite in macrophages resembling *Histoplasma*

### *Bone marrow biopsy*

increased histiocytes with intracellular capsulated organism morphologically consistent with *H. capsulatum* s/o histoplasmosis.

After the final diagnosis, the patient was managed with liposomal amphotericin B 3 to 5 mg /kg/day for 1 week (ideally, it should have been 2 weeks), which was stopped in view of rapidly declining renal function, serum creatinine reaching value of 5.1, the patient was continued on oral itraconazole 200 mg BD. Apart from this he was managed with higher antibiotics based on susceptibility testing, injection human albumin, various blood products, other symptomatic management, nutritional support and physiotherapy.

Patient showed remarkable improvement after antifungal medications were started, was weaned off from the ventilator, the tracheostomy tube removed and regained speech fluency after a few days. He was discharged successfully on oral itraconazole 200 mg BD to be continued for 1 year and advised monitoring of liver and renal function tests.

## Discussion

Considering this case report, since disseminated histoplasmosis is not a commonly encountered entity before coming to our hospital, during an initial patient presentation, a diagnosis of pancytopenia with hepatosplenomegaly was made at a private facility where the patient was admitted firsthand, and all the relevant investigations were done, some specific tests were also performed to rule out common infectious conditions, including pulmonary tuberculosis, immunodeficient conditions like HIV-AIDS. The patient showed no clinical improvement with empirical treatment and supportive care, and the patient's condition kept deteriorating further.

Then he again switched to another private hospital where, in view of his dull and drowsy condition along with severe respiratory distress, he was intubated and taken on mechanical mode of ventilation, and in view of prolonged respiratory support, he was tracheostomized, higher antibiotics were started based

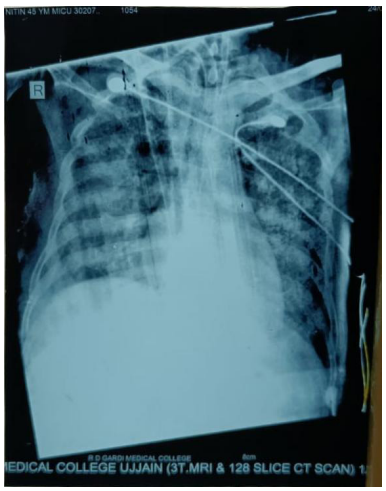


**Figure 2:** Chest x-ray

**Table 1:** Investigations

| | | |
|---|---|---|
| Cbc | Hb | 6.8 g/dl |
| | Rbc | 2.50[$10^6$/uL] |
| | Wbc | 3.2[$10^3$/uL] |
| | Platelet | 26[$10^3$/uL] |
| | Esr | 12 mm in one hour |
| Renal function test | Urea | 78.1 mg/dl |
| | Creatinine | 3.5 mg/dl |
| Liver function test | Total bilirubin | 1.3 mg/dl |
| | Albumin | 3.0 g/dl |
| | Sgot | 34.9 U/L |
| | Sgpt | 20.4 U/L |
| | Alp | 662 U/L |
| Serum electrolytes | Sodium | 126.5 mmol/l |
| | Potassium | 3.7 mmol/l |
| Urine analysis | Pus cells | 46 |
| | Sugar | Present |
| Retic count | | 4% |
| Hba1c | | 5.5% |
| CD4 COUNT | | 159 |
| (6weeks apart) | | 198 |
| CRP | | 48.8 |
| HIV 1 and 2 | Non-reactive | |
| HbsAg | Non-reactive | |
| Malaria antigen | Negative | |
| Typhidot-IgG,IgM | Negative | |
| Dengue – | Negative | |
| Ns1 antigen | Negative | |
| IgG, IgM | | |
| Procalcitonin | 0.72 (at admission) | |
| | 0.06 (at discharge) | |

on culture sensitivity of blood and sputum, injection human albumin. In view of persistent fever, altered consciousness and since no improvement in clinical condition occurred, a bone marrow examination was performed, which demonstrated the presence of *Histoplasma* in both aspiration and marrow biopsy, which clinched the diagnosis of disseminated histoplasmosis and then relevant antifungal, i.e., liposomal amphotericin B was started. Patient was weaned off from the ventilator and was able to maintain saturation. Still, it had to be withdrawn after 5 days due to rapidly declining renal function, and again patient landed up in respiratory distress and volume overload condition, leading to reintubation.

After such a long and hefty clinical stay patient was discharged from that hospital and then finally referred to C R Gardi Hospital Ujjain, where he was received in a very poor clinical condition with tracheostomy in situ, on the mechanical mode of ventilation and infusion Lasix. Here, he was managed with culture-sensitive antibiotics, antifungal agent Itraconazole, diuretics, prokinetic agents, potassium supplementation, and other supportive measures, along with strict clinical monitoring. Apart from this, he had continuous access to limb and chest physiotherapy and proper nutritional supplementation.

Following this, the patient had drastic clinical improvement as evidenced from his weaning off ventilator support and subsequent removal of tracheostomy tube with suture closure, regaining of voice, all metabolic parameters improved, relief from respiratory distress, regaining of appetite and improvement in overall health status.

The clinical spectrum of histoplasmosis ranges from asymptomatic infection to life-threatening illness, from acute pulmonary then chronic/cavitatory pulmonary to progressive disseminated histoplasmosis.[1,8] Pulmonary involvement is present in up to 90% of cases and the most common chest X-ray finding is prominent bronchovesicular markings as seen in our case.[5] Once inside the body, histoplasma can spread to multiple organ systems, causing a disseminated infection.[7] The clinical presentation of pulmonary and disseminated histoplasmosis can be easily confused with tuberculosis, sarcoidosis, malignancy and other fungal infections (*Aspergillosis, Blastomycosis*).[1] PDH is typically seen in immunocompromised individuals, who account for ~70% of cases. Disseminated infections have an acute, rapidly fatal course leading to diffuse interstitial lung infiltrates and multiorgan dysfunction. Common manifestations include fever, weight loss, hepatosplenomegaly, and thrombocytopenia.

Idiopathic CD4 lymphocytopenia (ICL) is a rare syndrome with absolute CD4 T lymphocyte count <300/μLor < 20% of total T cells on two occasions(6 weeks apart) in the absence of HIV 1 and 2 infection and other immunosuppressive conditions,[4] as evident in our case, moreover we ruled out the common immunocompromised conditions including his immunoglobulins (IgG, IgA, IgM) and complement levels which were within normal limit.[8] HIV 1 and 2 and other viral infections (Hepatitis B, C) that can cause CD 4 cell lymphopenia were also negative. Common diagnostic tests include the detection of *Histoplasma* antigen in BAL fluid or serum, *Histoplasma* serology (IgG and IgM antibodies), and fungal stains of cytopathology or biopsy materials are required in disseminated infections.(6) Antigen levels correlate with the severity of illness in PDH and can be used to follow disease progression, as levels predictably decrease with effective therapy.

## Conclusion

Histoplasmosis in not uncommon in India and may well be an under-recognized disease(6). Tests for *Histoplasma* antigen and serology are not commercially available

in India and therefore, the true disease burden could be even higher. The association of histoplasmosis and Idiopathic CD4 Lymphocytopenia is rare.[4]

We suggest that CD4 count should be done in all cases of histoplasmosis, even in HIV-negative individuals to rule out Idiopathic CD4 Lymphocytopenia.[4]

It should invariably be considered in the differential diagnosis if male patients present with prolonged fever, adrenal enlargement, hepato-splenomegaly, oral ulcers and granulomas on HPE.[5,6] Confirmation of the diagnosis requires histopathology, including fungal staining of granulomas and/or culture of appropriate samples.[8] Treatment with itraconazole leads to an excellent outcome in the majority of patient.

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