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**Case report**

# Unmasking Disseminated Histoplasmosis Immune Reconstitution with Adrenal Insufficiency in a HIV Infected on HAART

**Arvind M N [1], Bhargav V Bhat [2], Monika N [2]**

[1]Professor, Department of General Medicine, Shri Atal Bihari Vajpayee Medical College and Research Institute Bangalore, Karnataka, India
[2]Post Graduate, Department of General Medicine, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

*Corresponding Author: Bhargav V Bhat; *bhrgvbhat@gmail.com*

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## Summary

Histoplasmosis is a fatal but rare infection caused by Histoplasma Capsulatum which is Dimorphic fungi found in soil. Incidence of Histoplasmosis is in HIV infected is around 2-5% while its only <0.05% in Non-HIV infected Individuals. In our case Patient with initial CD4 Counts of 22 was started on HAART therapy after ruling out common opportunistic infections like Tuberculosis etc. 7 months later patient presented with Features suggestive of Adrenal insufficiency (Fever, Diarrhea , vomiting , Dizziness, Hypotension confirmed with relevant tests) . Chest X-ray revealed B/L Nodular opacities and Lymph node biopsy Suggested Intranuclear yeast like inclusions s/o Histoplasmosis. Patient was treated with Liposomal Amphotericin B for 10days which showed complete resolution of Chest X-ray B/L nodular opacities along with Clinical Improvement and Patient was later discharged

## Introduction

Histoplasmosis is a fatal but rare infection caused by Histoplasma Capsulatum which is Dimorphic fungi found in soil [1]. Incidence of Histoplasmosis is in HIV infected is around 2-5% while its only <0.05% in Non HIV infected Individuals [2]. While Evaluating and Screening an HIV infected individual it is important to rule out all possible Common opportunistic infections like Tuberculosis, Toxoplasmosis, Hepatitis B, Hepatitis C, Cytomegalovirus, Histoplasma, and Cryptococcus. Especially in a patient with Very Low CD4 Count < 100 it is very much important to rigorously screen for all common opportunistic infection especially Histoplasmosis and Coccidiodes [3]. Inadequate screening for opportunistic infections especially in patients with CD4 counts less than 100 can have disastrous consequence of Unmasking IRIS or Progression of Opportunistic infections later.

## Case Presentation

A 36year Old male presented with Fever since 7 days, Loose stools since 3 days, Vomiting since 1 day. He had a significant Past Medical History of Genital herpes and oral Candidiasis where he was diagnosed to have HIV with CD4 counts of 22 and started on ART TLD regimen after ruling out Tuberculosis 7 months back. He was a known case of non-Insulin dependent Diabetes Mellitus since 1 year and was on Oral Hypoglycemic Agents. He was also on Cotrimoxazole prophylaxis therapy.

On admission His vitals were PR-98bpm, BP- 70/40mmHg, RR-28 breaths/min (tachypneic), Spo2- 96% room Air. He was poorly built and nourished with Weight of 46Kg, Height-166cm (BMI-16.8).

Head to toe examination revealed Multiple enlarged firm, nontender lymph nodes in Bilateral cervical and axillary areas. Hyper pigmented lesions in the tongue, buccal mucosa and palmar surface of both hands.

Systemic Examination was unremarkable except for Crackles in BL lung Fields and Splenomegaly of 10cm.

**Figure 1**

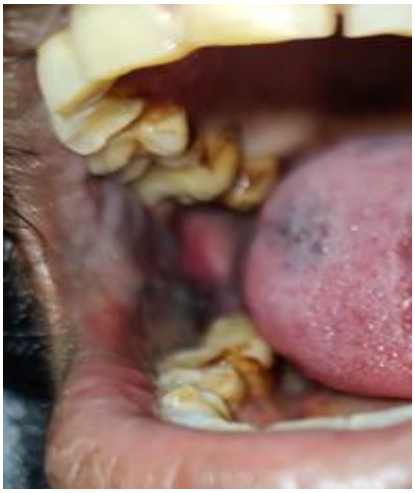

**Figure 2**

**Figure 3**

**Figure 1,2,3: Showing Mucosal and Skin Hyperpigmentation**

## Investigations

CBC revealed Total Leukocyte counts of 40700, CD4 counts were 222, Deranged RFT- Urea/Creatinine - 81/4.4 Procalcitonin >100, D-Dimer >1050 with Chest X-Ray revealing B/L nodular infiltrates and HRCT THORAX-Centrilobular nodules and multifocal ground glass opacities in B/L lung fields with Minimal left pleural effusion. Patient was hence diagnosed to be in Sepsis with Septic shock with Community Acquired pneumonia but Blood culture, Urine culture, Sputum culture returned Negative for bacterial growth, Sputum AFB and GeneXpert were negative for MTB. Lymph node FNAC from Neck and Axilla - H&E showed Yeast like inclusions within Neutrophils which was confirmed by PAS staining as Histoplasma.

Patient was started on IV Antibiotics and IV Liposomal Amphotericin B showed improvement clinically but hypotension didn't improve with resolving sepsis , 2D ECHO was done and showed Normal LV function with Ejection Fraction of 57% , Early morning Cortisol Levels were 13.5, adrenal insufficiency was suspected due to low levels in the presence of sepsis and COSYNTROPIN stimulation test was done which failed to show raise in S. cortisol levels (14.3) MRI ABDOMEN which suggested Splenomegaly (13.5cm) with associated multiple hyperintense lesions noted within the splenic parenchyma but with grossly Normal adrenal size. S. ACTH was high 63.20pg/mL with Normal S. RENIN levels 1.12ng/ml/hr with failure of rise in ACTH levels after CO-SYNTROPIN stimulation test (Serum Cortisol 14.3) confirming the Primary adrenal insufficiency.

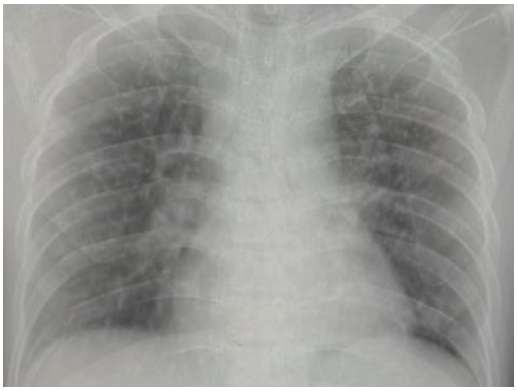

**Figure 4- Chest X-Ray Showing B/L nodular opacities**

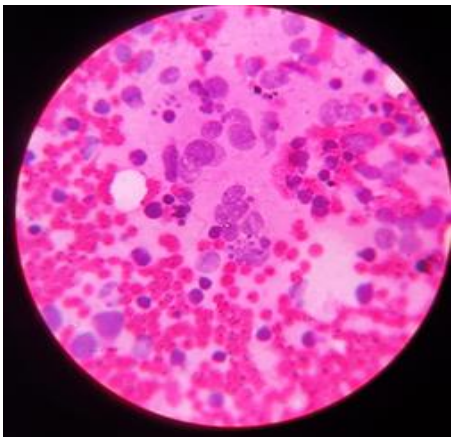

**Figure 5**

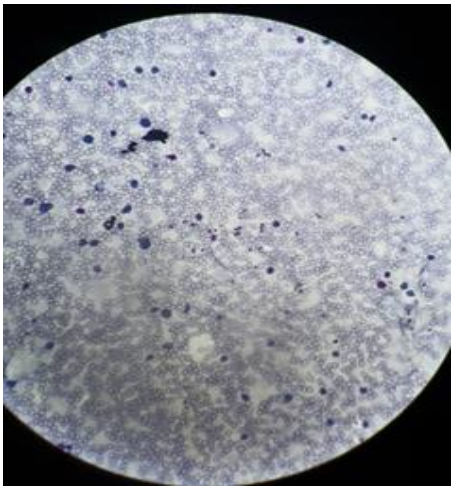

**Figure 6**

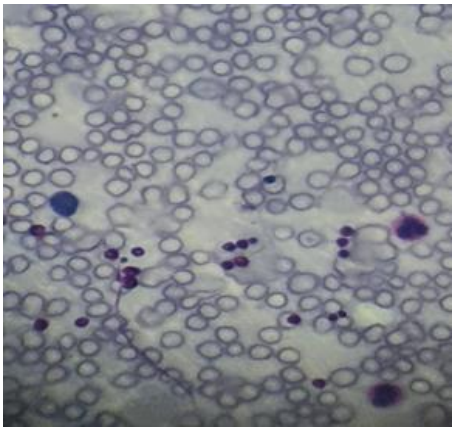

**Figure 7**

**Figure 5,6,7: Showing Yeast like inclusions inside within Neurtophil confirmed by PAS staining**

## Differential Diagnosis

Initially we considered Miliary TB as first diagnosis considering Chest Xray suggesting B/L nodular infiltrates but Sputum and FNAC GeneXpert Ruled out MTB. FNAC Lymph node was suggestive of Histoplasmosis. Patient Started on IV liposomal Amphotericin B with Resolution of nodular infiltrates on chest x-ray and Clinical Improvement Confirmed disseminated Histoplasmosis. Patient was started on Fludrocortisone in view of Adrenal insufficiency after which Blood Pressure started to improve. Presentation with features suggestive of worsening Opportunistic infection i.e. Histoplasmosis with Immunological Improvement with CD4 222 was suggestive of Unmasking IRIS

## Treatment And Outcome

Standard Treatment for Histoplasma includes 7-14 days of Injection Liposomal Amphotericin B 3-5mg/kg/day followed by Oral Itraconazole 200mg BD for 12months. We followed the Standard treatment Protocol with IV Liposomal Amphotericin B along with IV antibiotics for the Sepsis part. There was significant improvement in clinical condition of the patient as evidenced by resolution in Chest X-ray

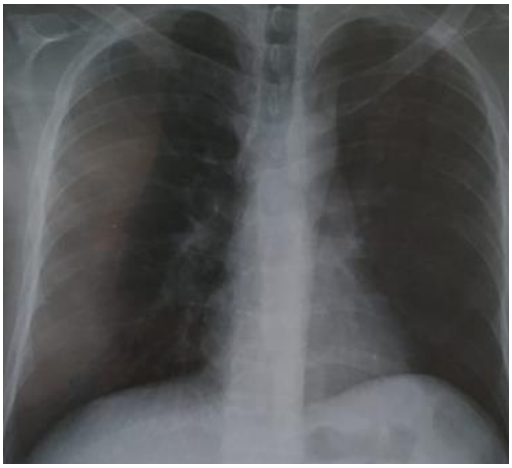

**Figure 8: Chest X-ray - PA showing resolution of nodular opacities post Treatment**

## Discussion

Diagnosis of Histoplasmosis can be based on clinical signs and symptoms, chest X ray, blood and bone marrow smear examination, histopathology, fungal culture, serology test such as complement fixation test, immunodiffusion, and histoplasmin skin test. Tests for histoplasma antigen and serology are not commercially available in India.

Histoplasma skin testing was the earliest diagnostic modality but has limited value as no longer reagents available [4,5]. Serology test in HIV patient has limited value because antibody production in these patients are decreased. Diagnostic Serological test would be Direct immunofluorescence in HIV patients. Prime investigating modality would be Histopathology as it provides conclusive evidence of disease [6]. Histopathological examination of the infected tissue usually demonstrates Numerous small (1–2 µ in diameter) yeast like microorganisms surrounded by the characteristic clear halo may be seen within macrophage, multinucleate giant cells, or within fibrous tissue in a noncaseating granulomatous inflammation [7].

Special stains such as Gomori methenamine silver (GMS) or PAS are required to confirm the organism in tissues. Fungal culture remains a gold standard diagnostic test. Culture is done on enriched agar base [8].

In our study, the diagnosis of histoplasmosis was made by FNAC and fungal cultures of appropriate specimens. On histopathology examination, patient had typical intracellular yeast like fungal organisms with negative acid-fast bacilli stains.

In patients with Disseminated Histoplasmosis Mortality with Antifungal agents reduces to < 25%, without Treatment mortality can be as high as 80-100% [9].

Amphotericin B is preferred for patients with severe or moderately severe progressive disseminated histoplasmosis with liposomal amphotericin B as an option in case of renal dysfunction [10,11].

Itraconazole is the drug of choice for treatment of patients with less severe illness [10].

## Learning Points

- Histoplasmosis is not an uncommon disease in India and may well be an under-recognized disease cause of lack of simple diagnostic tests.
- It should be considered in the differential diagnosis of male patients with prolonged fever,respiratory distress, adrenal Enlargement or f/s/o adrenal insufficiency, hepato-splenomegaly, oral ulcers and granulomas on HPE, especially to be suspected if there is a lack of response to empiric ATT.
- Diagnosis can be established with histopathology including fungal stains of granulomas, and/or cultures from appropriate specimens
- Treatment with Amphotericin B or Itraconazole leads to an excellent outcome in the majority of patients

## Conflict of interest

The authors declare no conflict of interest

## Funding

None

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