A Rare Case of Adrenal Insufficiency due to Histoplasmosis

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Summary
A 60 years old male an businessman living in Narnaul district, Haryana, known Hypertensive and Diabetic was admitted in SDMH with complains of severe generalized weakness, diffuse abdominal pain and H/O intermittent low grade fever for 4 months with H/O of weight loss. There was also complain of blackish discolouration of skin over the face, knuckles, elbow, buccal mucosa and chest which had developed over the last month. With differential diagnosis of tuberculosis and malignancy initial workup was done. The initial workup revealed primary adrenal insufficiency and bilateral adrenal space occupying lesion. Further investigation was done and finally on histopathological examination Histoplasmosis was diagnosed and patient was treated with antifungal with clinical recovery.

Our case was rare presentation of isolated adrenal histoplasmosis with adrenal insufficiency in a immunocompetent host in north western region of Rajasthan.

Introduction
Histoplasmosis is a systemic type of endemic mycosis caused by Histoplasma capsulatum which has a worldwide distribution. It is a thermally dimorphic fungus which exists in yeast form inside the human body and at 37°C and mold form in the environment and at 25°C–30°C. Usually, infection by Histoplasma occurs by the inhalation of microconidia into alveoli, but infection may also occur by other routes such as fomites, direct inoculation, solid organ transplant, and sexual contact.[¹] However, as a result of host immune response, the growth of yeasts is stopped within 1–2 weeks of exposure, and delayed type of hypersensitivity to Histoplasma antigens develops after 3–4 weeks of exposure.[²] Disseminated histoplasmosis is the extrapulmonary form of histoplasmosis and usually affects immunocompromised and immunosuppressed individuals such as patients with acquired immunodeficiency syndrome (AIDS), post transplant patients, and patients with serious underlying disorders. Disseminated histoplasmosis may involve various organ systems of our body such as central nervous system, ocular system, gastrointestinal tract, and genitourinary tract. However, most of the patients with disseminated histoplasmosis presents with bilateral adrenal masses, and adrenal gland is involved in 80% of the cases.[³] The incidence of hypoadrenalism amongst these group of patients is rare and was reported to be ranging between 7 to 20 %(Subramanian et al., 2005; Rajesh et al., 2010). [⁴,⁵] Hence, a high index of suspicion is
prudent as the presentation may mimic other chronic infections or malignancy especially in the elderly or the immunosuppressed host (Jaiswal et al., 2011)[6]

Hereby, We report a case of an elderly immunocompetent man with bilateral adrenal histoplasmosis with features of primary adrenal insufficiency who presented with vague symptoms.

**Case Presentation**

Mr. Harsh Vardhan Garg, 60 years old male an businessman living in Narnaul district, haryana, hypertensive, Diabetic, non smoker and non alcoholic was admitted in SDMH with severe generalized weakness , diffuse abdominal pain and history of intermittent low grade fever for 4 months with about 12-15 kg weight loss in last 4 months. There was also complain of blackish discoloration of skin over the face, knuckles, elbow, buccal mucosa and chest which had developed over the last month.

On examination vitals were stable and systemic examination revealed presence of shifting dullness. On Cutaneous examination there were multiple black patches, flat, non itchy and well demarcated, over the face, knuckles, elbow, buccal mucosa and chest. He was evaluated thoroughly & relevant investigation done.

Relevant findings on initial workup was raised ESR, Hypoalbuminemia and Hyponateremia .On ultrasound abdomen there was hepatomegaly with coarse ecotexture and increased periportal ecogenecity ,moderate ascites and bilateral adrenal space occupying lesion .Echo, ECG and chest x-ray were all normal. HIV and hepatitis B and C serology were negative too. For further evaluation cortisol, ACTH and CECT abdomen was done, which revealed low cortisol with raised ACTH and bilateral adrenal enhancing nodules? Granulomatous ?? metastatic. Tuberculosis work up was negative as well. Then he underwent image guided FNAC of adrenal glands & was diagnosed with bilateral Fungal Infection compatible with Histoplasmosis. Other relevant work for like ascitic tap and upper GI endoscopy was done which were compatible with NASH related CLD and negative for malignancy.

Patient was treated systemic antifungal that is Itraconazole & other symptomatic medication by multidisciplinary team. Patient’s condition improved over the next 5 days & was discharged with in stable condition. With the given treatment patient showed gradual improvement in appetite, there were minimum episode of fever and weight gain in next few follow-ups over a period of 3months.The patient was advised to continue medicine for duration of 1 year.

![Figure 1](image-url)
**Discussion**

Histoplasmosis is an infectious granulomatous disease caused by intracellular dimorphic fungus *Histoplasma Capsulatum*[^4^–^5^]. Humans get infected by airborne spores of birds or bat’s excreta[^4^–^5^]. The disease may be classified as Acute, Chronic, and Disseminated Histoplasmosis is rare occurring mostly in acute rather than chronic forms, however, the frequency of dissemination in Acute Histoplasma infections is 1:2000[^6^]. Most patients who develop acute infection are immunocompromised. Adrenal involvement by histoplasmosis may occur during the active course of dissemination It could be either a part of disseminated form in immunosuppressed patients or may occur as a localized adrenal disease. Godwin et al. reported acute adrenal crisis in 7% of patients presenting with disseminated histoplasmosis[^7^].

The geographic distribution of histoplasmosis is related to the humid and acidic nature of the soil in the endemic areas. Soil enriched with bird or bat droppings promotes the growth and sporulation of Histoplasma. Disruption of soil containing the organism leads to aerosolization of the microconidia and exposure of humans nearby. Activities associated with high-level exposure include spelunking, excavation, cleaning of chicken coops, demolition and remodeling of old buildings, and cutting of dead trees. Most cases seen outside of highly endemic areas represent imported disease, e.g., in Europe, histoplasmosis is diagnosed fairly often, mostly in emigrants from or travelers to endemic areas on other continents. The epidemiology of histoplasmosis is changing as a result of global climate changes and with the continued expansion of at-risk populations and the acceleration of intercontinental and international travel that brings this infection to areas of the world that are not known to be endemic. The population at risk for histoplasmosis continues to grow as a result of increasing numbers of patients receiving immunosuppressive therapies for autoimmune disorders, cancers, and organ transplants.

The clinical spectrum of Disseminated Histoplasmosis ranges from an acute, rapidly fatal course—with diffuse interstitial or reticulonodular lung infiltrates causing respiratory failure, shock, coagulopathy, and multiorgan failure—to a subacute or chronic course with a focal organ distribution. Common manifestations include fever, weight loss, hepatosplenomegaly, and thrombocytopenia. Other findings may include meningitis or focal brain lesions, ulcerations of the oral mucosa, gastrointestinal ulcerations and bleeding, and adrenal insufficiency. Fungal culture remains the gold standard diagnostic test for histoplasmosis. However, culture results may not be known for up to 1 month, and cultures are often negative in less severe cases. Fungal stains of cytopathology or biopsy materials showing structures resembling *Histoplasma* yeasts are helpful in the diagnosis of PDH, yielding positive results in about half of cases. Culture and pathology are no longer...
performed in most patients because diagnosis is more often established by antigen detection and/or serology, more rapidly and without subjecting the patient to invasive procedures. But in our case we have gone for histopathological diagnosis. Serologic tests, including immunodiffusion (ID), complement fixation (CF), and IgG and IgM enzyme immunoassay (EIA), are useful for the diagnosis of histoplasmosis, especially in immunocompetent patients. One month may be required for the detection of antibodies after the onset of infection by ID or CF, but antibodies may be detected earlier by more sensitive methods (EIA). Limitations of ID and CF, however, include insensitivity early in the course of infection and reduced sensitivity in immunosuppressed patients, especially those receiving immunosuppression for organ transplantation. Also, antibodies may persist for several years after infection. Positive results from past infection may lead to a misdiagnosis of active histoplasmosis in a patient with another disease process. The preferred treatments for histoplasmosis include the lipid formulations of Amphotericin B in severe cases and Itraconazole in others. Posaconazole and Isavuconazole are alternatives for patients who cannot take Itraconazole.\[8\] Disseminated histoplasmosis may affect reticuloendothelial system, lungs, gastrointestinal tract, urinary tract, CNS, bone marrow, and adrenal glands. The adrenal glands are frequently involved through hematogenous route in disseminated histoplasmosis mainly in immunocompromised patients such as AIDS patients, transplant recipients, those with hematologic malignancies, and patients on corticosteroids.

Although rare, adrenal histoplasmosis has been reported in immunocompetent patients in India as well as in other countries. [Table 1] depicts the reports of adrenal histoplasmosis in otherwise immunocompetent patients from India\[9\]

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Place</th>
<th>Immune status</th>
<th>Diagnostic method used</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 years/male</td>
<td>Bhopal</td>
<td>Immunocompetent</td>
<td>FNAC of adrenal mass</td>
<td>Antifungal therapy (exact drug not mentioned in the article)</td>
<td>Good</td>
</tr>
<tr>
<td>57 years</td>
<td>Vellore</td>
<td>All immunocompetent (diabetes mellitus in four patients)</td>
<td>Histopathology and fungal culture</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>45 years/male</td>
<td>Delhi</td>
<td>Nodular</td>
<td>Skin biopsy of papules over chest and cypopathological examination of pus aspirate from adrenal abscess</td>
<td>Intravenous amphotericin B, repeated aspirations of adrenal gland with ultrasound monitoring of amphotericin B and open drainage of adrenal gland abscess followed by maintenance itraconazole</td>
<td>Good</td>
</tr>
<tr>
<td>46 years/female</td>
<td>Chhatrapur</td>
<td>Diabetes for 7 years</td>
<td>FNAC of pelvis ulcer</td>
<td>Itraconazole (300 mg BD) for 6 months</td>
<td>Good</td>
</tr>
<tr>
<td>40 years/male</td>
<td>West Bengal</td>
<td>Immunocompetent</td>
<td>FNAC and culture also positive for Histoplasmos</td>
<td>Intravenous liposomal amphotericin B followed by oral itraconazole for one and a half months</td>
<td>Expired</td>
</tr>
<tr>
<td>70 years</td>
<td>West Bengal</td>
<td>Diabetes for 10 years</td>
<td>FNAC of nodules on face</td>
<td>Itraconazole 400 mg/day</td>
<td>Defined treatment</td>
</tr>
<tr>
<td>50 years/male</td>
<td>Delhi</td>
<td>Immunocompetent</td>
<td>Laparoscopic adrenalectomy followed by oral itraconazole (200 mg twice a day) with low-dose prednisolone (3 mg/day)</td>
<td>Itraconazole 400 mg/day</td>
<td>Good</td>
</tr>
<tr>
<td>37 years/male</td>
<td>Lucknow</td>
<td>All patients immunocompetent (diabetes in three patients, HIV not tested in three patients)</td>
<td>FNAC</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>61 years/male</td>
<td>Delhi</td>
<td>Immunocompetent</td>
<td>FNAC of adrenal mass</td>
<td>Amphotericin B</td>
<td>Good</td>
</tr>
<tr>
<td>52/male</td>
<td>Chandigarh</td>
<td>All immunocompetent; one patient with diabetes; and two alcoholics</td>
<td>Histopathological examination of adrenal tissue and adrenalectomy; FNAC of adrenal mass</td>
<td>Amphotericin B and/or itraconazole</td>
<td>Good</td>
</tr>
<tr>
<td>61 years/male</td>
<td>Bilal</td>
<td>Immunocompetent</td>
<td>Skin biopsy/culture negative</td>
<td>Amphotericin B</td>
<td>Good</td>
</tr>
</tbody>
</table>

FNAC: Fine needle aspiration cytology; BD: Twice a day.
The differential diagnosis of adrenal histoplasmosis includes primary adrenal malignancy, tuberculosis, adrenal blastomycosis, and adrenal coccidioidomycosis. In a country like India where tuberculosis is very common, it is often misdiagnosed as tuberculosis and the patient is put on antitubercular therapy. [10]

**In conclusion,** although rare but histoplasmosis can primarily affect adrenal gland causing adrenal insufficiency even in a immunocompetent host from non endemic regions like Rajasthan. Diabetes could be one of the risk factors predisposing to histoplasmosis which needs further research to be established. Early recognition and prompt treatment could lead to complete recovery without any complication in a immunocompetent host. Histoplasmosis should be kept in back of mind as a possible differential along with tuberculosis to vague symptoms like in our case even in non endemic regions of India.

**Take Home Messages**
1. Histoplasmosis can primarily affect adrenal gland.
2. Histoplasmosis can cause primary adrenal insufficiency.
3. Diabetes could be one of the risk factors predisposing to histoplasmosis in immunocompetent host.
4. Early diagnosis and prompt treatment is crucial.
5. Due to global connectivity these rare diseases can present at times in non endemic region and should be kept in mind so that they are not missed.

**References**