

Disseminated histoplasmosis with adrenal insufficiency in an immunocompetent adult – A case report

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ABSTRACT

Histoplasmosis is a rare and potentially fatal disease caused by *Histoplasma capsulatum*. The occurrence of disseminated histoplasmosis in immunocompetent individuals is rare. The presentation of disseminated histoplasmosis as adrenal insufficiency is extremely rare and associated with significant mortality. We describe the case of a 49-year-old patient who presented with fatigability, postural hypotension, a large tongue ulcer, and hypoglycemia. The patient was found to have adrenal insufficiency and on evaluation was diagnosed as histoplasmosis. He was subsequently given antifungals and his adrenal insufficiency improved with treatment.

Key words: Adrenal insufficiency, Histoplasmosis, Immunocompetent

Histoplasmosis is a rare and potentially fatal disease caused by dimorphic soil fungus *Histoplasma capsulatum* [1]. Incidence is 2–5% in patients with human immunodeficiency virus (HIV) infection and <0.05% in non-HIV patients. In patients with disseminated histoplasmosis, adrenal involvement occurs in 80–90% cases and the incidence of adrenal insufficiency in these patients is <10% [2]. Adrenal involvement with adrenal insufficiency as the presenting manifestation of the disease is rare in India. Here, we describe the case of a 49-year-old patient with adrenal insufficiency as the presenting symptom of histoplasmosis.


CASE REPORT

A 49-year-old male from North Kerala, belonging to the tribal community, presented with complaints of a significant loss of weight of 10 Kg over 3 months, anorexia, and fatigability for the past 3 months. He also complained of fever, which was low-grade and intermittent for 3 weeks duration. There was no history of cough, hemoptysis or contact with tuberculosis. He had nausea for the past 1 week, but there was no vomiting or abdominal pain. His urinary and bowel habits were normal. He was diagnosed to have diabetes mellitus 6 years back and was on indigenous treatment which was stopped recently in view of hypoglycemia.

On examination, the patient was emaciated with a body mass index (BMI) of 13 and had pallor. He was febrile with a temperature of 100°F. He also had a significant postural fall in blood pressure (BP), his supine BP was 120/70 mmHg, and standing BP after 3 min was 80/60mmHg. His respiratory system, cardiovascular system, and neurological examination were normal. He had a large ulcer with irregular borders and elevated margins on the tongue (Fig. 1a).

Investigations revealed anemia (hemoglobin 8gm/dl), normal total leukocyte counts, and elevated erythrocyte sedimentation rate (ESR 90 mm/hr). The patient had normal renal function tests, liver function tests, and normal serum potassium but hyponatremia (serum sodium 120 mEq/l). His blood and urine cultures were normal. The chest X-ray was also normal.

In view of the postural hypotension, hypoglycemia in a previously diabetic patient, and hyponatremia, a possibility of adrenal insufficiency was suspected, and the fasting cortisol value was 4 µg/dl (normal range 5–25 µg/dl). A cosyntropin test was done and it failed to show a rise in serum cortisol and the serum adrenocorticotropin hormone was high; hence, a diagnosis of primary adrenal insufficiency was made. Further, the workup for the causes of primary adrenal insufficiency was done. Autoimmune adrenalitis was unlikely in our patient. Workup for tuberculosis (chest X-ray and Mantoux) was negative. Screening for retroviral infection was also negative. An upper gastrointestinal endoscopy was also normal. Contrast-enhanced computed tomography scan of the abdomen showed a

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well-defined rounded non-enhancing lesion in the right suprarenal location of size 7.1×6.9× 8 cm, with coarse central calcification, along with moderate ascites, bilateral pleural effusion, and mild pericardial effusion (Fig. 1b). The possibilities considered were granulomatous infection (tuberculosis and histoplasmosis), ganglioglioma, and pheochromocytoma. An ultrasound-guided biopsy of the adrenal lesion and a tongue biopsy was also taken.

The histopathology of both the specimens revealed granuloma formation with the cytoplasm of the macrophages loaded with small rounded yeast forms of a fungus suggestive of *H. capsulatum* (Fig. 1c). Further, a Gomori methenamine silver (GMS) stain was done, which was positive (Fig. 1d). For confirmation of the diagnosis, a Histoplasma urine antigen was done, which was also positive. Hence, a diagnosis of disseminated histoplasmosis was made considering the histopathological findings of *H. capsulatum* in both adrenal biopsy, tongue ulcer biopsy, positive GMS stain in both, and positive Histoplasma urine antigen test.

Our patient was treated with liposomal Amphotericin B (5 mg/kg/day) for 2 weeks followed by itraconazole for 12 months. During follow-up, a repeated serum cortisol level was within the normal range (serum cortisol 22 µg/dl). With treatment, the patient started gaining weight and his electrolytes normalized.

DISCUSSION

Histoplasmosis is asymptomatic or self-limited in a majority of the patients, but some individuals develop acute pulmonary infection or severe, and progressive disseminated disease [3]. Most patients with disseminated histoplasmosis have underlying conditions that impair their ability to defend against intracellular pathogens, but 20%–70% of patients, similar to our case, lack obvious risk factors for dissemination [3]. Risk factors for disseminated histoplasmosis include extremes of age, transplant

recipients, immunosuppressive medications, and retroviral infection. A more indolent type of disseminated histoplasmosis is seen in otherwise healthy individuals, who may present with oral ulceration. Clinical spectrum of the disease can vary from primary pulmonary histoplasmosis, primary cutaneous histoplasmosis, and disseminated histoplasmosis. Disseminated histoplasmosis in immunocompetent adults is rarely reported in the literature.

Abdominal imaging usually showed enlargement of the liver, spleen, lymphadenopathy, and adrenomegaly. Adrenal involvement can be unilateral or bilateral but most commonly presents with bilateral adrenal masses with varied imaging features such as peripheral rim enhancement, central hypoattenuation, internal septations, and calcifications [2]. In our patient, only unilateral adrenal involvement was seen on imaging but with severe adrenal insufficiency which is unusual. Kumar *et al.* described a case series of nine patients, among which eight patients had bilateral adrenal masses and one had a unilateral adrenal mass. Imaging features were variable. All adrenal masses were hypoechoic on ultrasound, homogeneous in five, and heterogeneous in four patients. All adrenal masses were hypodense on CT, homogeneous in four, and heterogeneous in two. Heterogeneous enhancement was seen in three, homogeneous enhancement in two, and no enhancement in one patient. Magnetic resonance imaging in three patients showed that the masses were of variable signal intensity on all pulse sequences [4].

Diagnosis of adrenal histoplasmosis can be confirmed by tissue diagnosis [5]. Fine-needle aspiration cytology can suggest the diagnosis which can be further confirmed by culture, polymerase chain reaction, and urine antigen tests. The gold standard for diagnosis is fungal culture. These tests can be helpful in differentiating histoplasmosis from tuberculosis [5]. *H. capsulatum* is an intracellular dimorphic fungus which is commonly seen within the cytoplasm of the macrophages and exhibit narrow-based budding [6]. Although the organism can sometimes be demonstrated by hematoxylin and eosin stain, it is better visualized using methenamine silver or periodic acid-Schiff stains.

Antifungal agents reduce mortality to <25% in patients with disseminated histoplasmosis, whereas mortality without treatment can be as high as 80–100%. Conventional amphotericin B (0.5–1 mg/Kg) for 1–2 weeks followed by itraconazole (200 mg twice daily for at least 12 months) is preferred for the patients with severe or moderately severe disseminated histoplasmosis. Liposomal amphotericin B (3–5 mg/kg) is an option in patients with renal dysfunction [7,8].

A similar case of adrenal histoplasmosis in an immunocompetent Srilankan male has been previously described who also improved with antifungals [9]. Another case series described four cases of Addison's disease due to adrenal histoplasmosis, of which one person died [10]. Two case reports of histoplasmosis presenting as adrenal masses but without adrenal insufficiency had been described by Vyas *et al.* and Wahab *et al.* [3,11]. This case is unique due to the presentation of the patient with unilateral adrenal involvement, adrenal insufficiency, and the presence of the tongue ulcer.

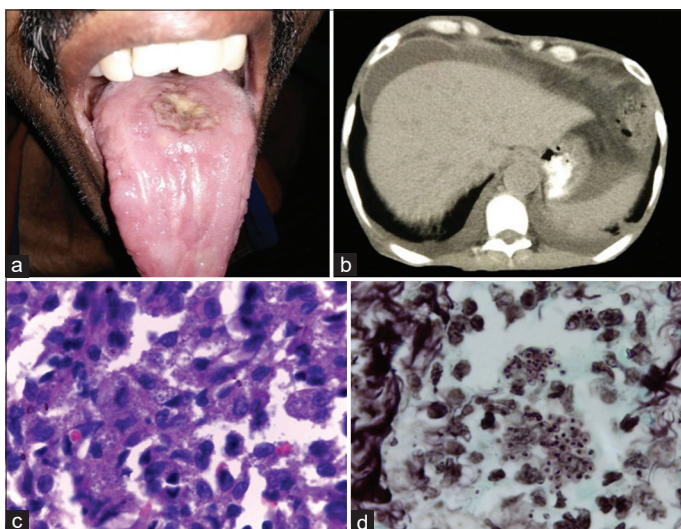


Figure 1: (a) Photograph of tongue ulcer of the patient; (b) CT scan showing adrenal calcification; (c) Microphotograph of H&E-stained section of adrenal biopsy showing granuloma formation with cytoplasm of the macrophages loaded with small rounded yeast forms of a *Histoplasma capsulatum*; and (d) Microphotograph of methenamine silver-stained section showing the same yeast forms.

Furthermore, adrenal insufficiency as a presenting manifestation of histoplasmosis is rare in India and we were able to isolate the organism from both the tongue ulcer and adrenals.

CONCLUSION

Disseminated histoplasmosis can rarely occur in immunocompetent young adults. In patients with adrenal insufficiency, histoplasmosis should be ruled out and early treatment can significantly reduce the mortality in such cases.

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