Case Report:

Histoplasmosis presenting as hypoadrenalism

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ABSTRACT

Histoplasmosis is considered to be rare in India. Adrenal involvement is common in disseminated disease but may be the only site of demonstrable disease sometimes. We describe the case of a 36-year-old lady with type 2 diabetes mellitus who presented with adrenal insufficiency in whom computed tomography and fine needle aspiration cytology helped in establishing the diagnosis. A high index of clinical suspicion and appropriate use of invasive diagnostic methods will be helpful in early diagnosis and institution of appropriate treatment.

Key words: *Histoplasmosis, Bilateral adrenal masses, Cortisol, Adrenal insufficiency*

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INTRODUCTION

Histoplasmosis, a granulomatous fungal disease caused by the intracellular dimorphic, saprophytic fungus *Histoplasma capsulatum* is acquired by the inhalation of mycelia fragments and microconidia.[1,2] Histoplasmosis is found world wide and is endemic in parts of the USA, West Indies, Africa and the Far East.[3] Most cases from India have been reported from the Gangetic plains.[4,5] Symptoms usually begin 10-14 days after exposure. The clinical spectrum of histoplasmosis ranges from asymptomatic infection to progressive disseminated histoplasmosis (PDH) depending upon the intensity of exposure and the immune status of the exposed individual.[1,6] Clinical presentation can, therefore, vary from an acute rapidly fatal course with diffuse interstitial or reticulo-nodular lung infiltrates causing respiratory failure, shock, hepatosplenomegaly and multi-organ dysfunction syndrome (MODS) to a more subacute course with a focal organ distribution involving liver, spleen, adrenals, muco-cutaneous regions and bone marrow.[1] Asymptomatic adrenal involvement has been described in patients with disseminated histoplasmosis.[5] Isolated adrenal involvement with adrenal insufficiency as the presenting manifestation of the disease is rare in India.

CASE REPORT

A 36-year-old lady, known to have type 2 diabetes mellitus for the preceding five years, presented to our hospital with 6 months history of on-and-off fever, loss of weight and appetite. On examination her general condition was poor and she had hyperpigmented palms and soles (Figures 1 and 2); her blood pressure was 100/70 mm of Hg. There was no evidence of lymphadenopathy or hepatosplenomegaly. The chest radiograph was normal. Laboratory investigations revealed persistently low blood glucose and serum sodium levels and normal serum potassium

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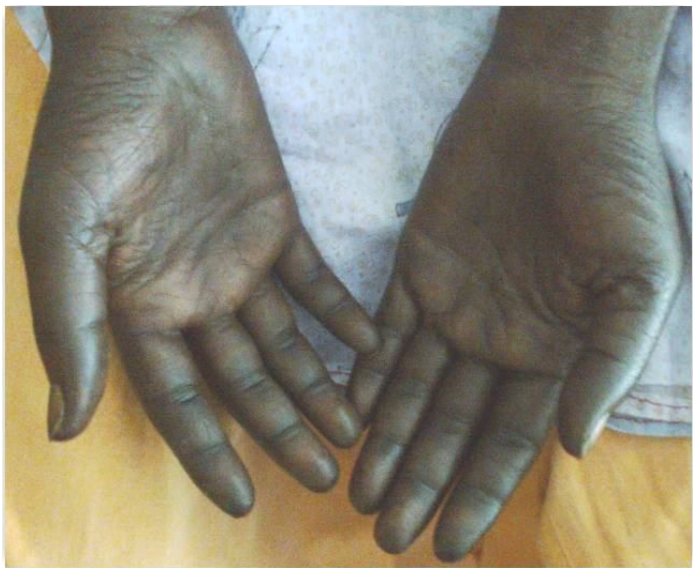

Figure 1: Clinical photograph showing hyperpigmentation of palms

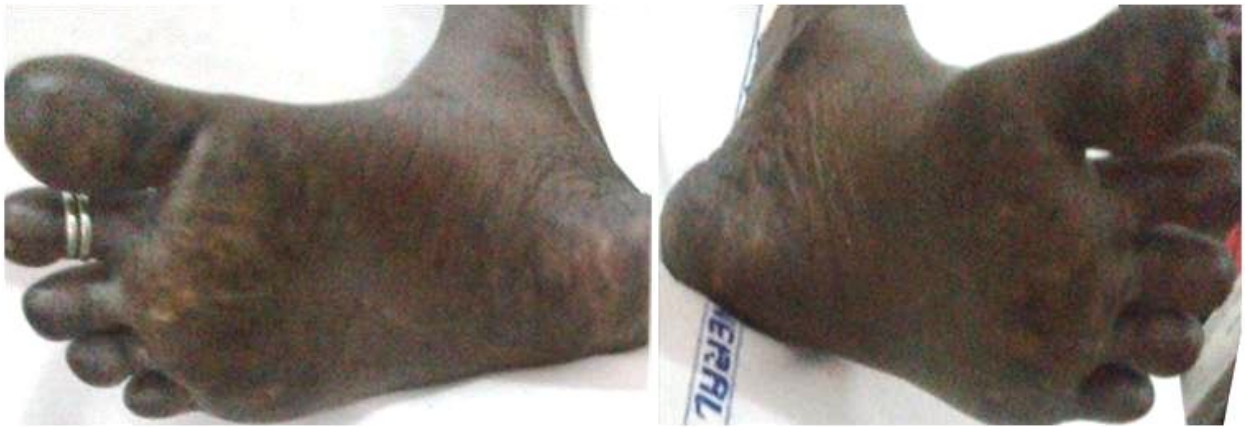

Figure 2: Clinical photograph showing hyperpigmenation of soles

levels. Serological testing for human immunodeficiency virus was non-reactive. The patient was worked up adrenal insufficiency. Fasting serum cortisol level was 118 nmol/L (normal = 138 - 690 nmol/L). Stimulation with 250 µg of cosyntropin [serum adrenocorticotropic hormone (ACTH)] revealed a serum cortisol level of 115 nmol/L at 30 minutes suggestive of lack of response; serum ACTH levels were elevated (334.5 pg/mL) suggestive of primary adrenal insufficiency. The patient was started on intravenous hydrocortisone (100 mg twice daily) and antibiotics. Abdominal ultrasonography revealed bilateral adrenal masses. Contrast enhanced computed tomography (CECT) of abdomen revealed bilateral adrenal masses with mesenteric lymphadenopathy (Figure 3). The diagnostic possibilities considered included granulomatous infections like tuberculosis and metastasis. Computed tomography (CT) guided fine needle aspiration cytology (FNAC) of adrenal masses was next done which on cytopathological examination revealed numerous neutrophils and macrophages with round to oval yeast forms of *Histoplasma capsulatum* (Figures 4A and 4B). In view of the above features, a diagnosis of adrenal histoplasmosis with hypoadrenalism was made and the patient was started on intravenous amphotericin B, initially at a dosage of 1 mg/Kg body weight that was later increased to 3 mg/Kg body weight). In spite

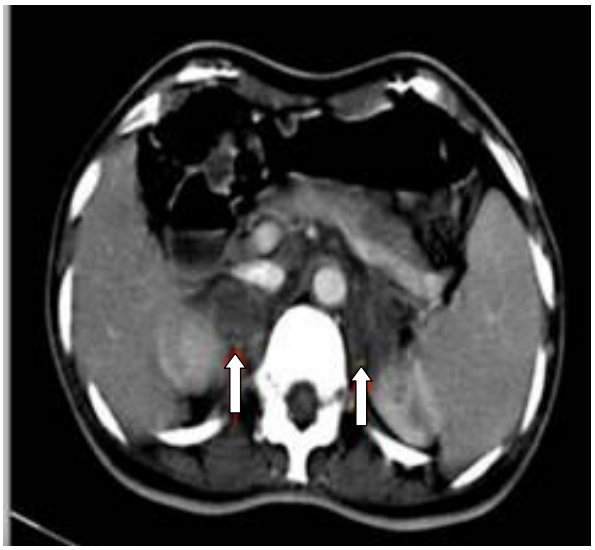

Figure 3: CECT abdomen showing irregular minimal enhancing lesions with central necrotic (arrows) areas in bilateral suprarenal regions

of all these efforts, the patient succumbed to her illness and died after three days.

DISCUSSION

Histoplasmosis is asymptomatic or self limited in majority of patients but some individuals develop acute pulmonary infection or severe and progressive disseminated disease. Disseminated histoplasmosis is a progressive extrapulmonary infection.[6] Haematogenous dissemination occurs in most patients during the acute infection before cellular immunity develops. Disseminated disease occurs in 1 in 2000 acute infections, especially in patients with acquired immunosuppression, such as, HIV infection/acquired immunodeficiency syndrome (AIDS), organ transplantation, treatment with anti-tumour necrosis factor-alpha agents or in patients at the extremes of age.[6]

Infection develops when histoplasma micro-conidia are inhaled into the lungs, where they germinate into yeast form. In patients with progressive disseminated infection organisms are confined to macrophages and rarely are seen growing freely within the tissue spaces. The organism can occasionally be seen in peripheral blood monocytes. Most patients with disseminated histoplasmosis have underlying conditions that impair their ability to defend against intracellular patho-gens. Despite several known predispo-sing conditions, 20%-70% of patients lack obvious risk factors for dissemination.[6] A more indolent type of disseminated histo-plasmosis is seen in otherwise healthy individuals. They usually present with either oral ulceration or hypoadrenalism.

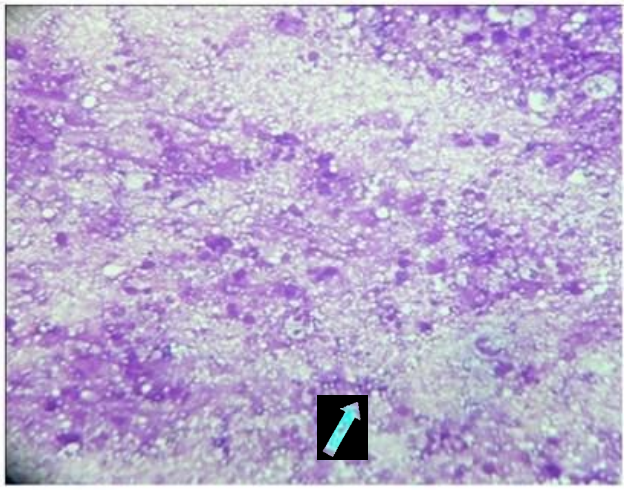

Figure 4A: Photomicrograph of FNAC from right adrenal mass showing numerous neutrophils and macrophages and round to oval yeast forms of *Histoplasma capsulatum* (arrow) (Leishman, × 400)
FNAC=fine needle aspiration cytology

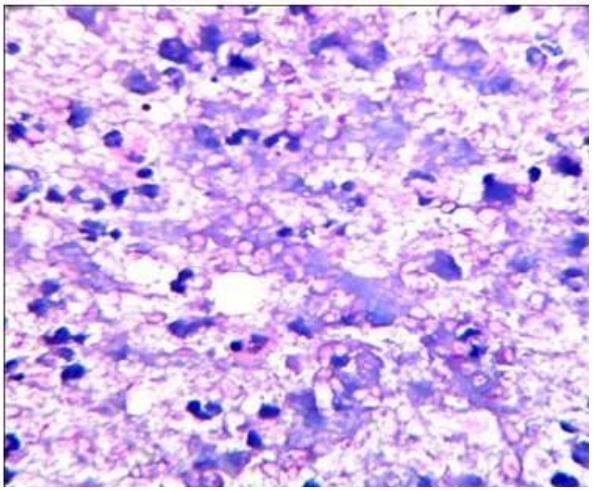

Figure 4B: Photomicrograph of FNAC from right adrenal mass showing numerous purple coloured yeast forms of histoplasma capsulatum (Periodic-acid Schiff × 1000)
FNAC=fine needle aspiration cytology

Adrenal histoplasmosis usually presents with bilateral adrenal masses with varied imaging features.[2] On ultrasonography, they may be uniformly hypoechoic or show heterogeneous echo pattern Bilateral symmetrical adrenomegaly with preservation of gland contour, central hypodensity with peripheral rim enhancement and presence of calcification has been described in CT.[2] In this case, CT revealed bilateral adrenal masses with central hypoattenuation and minimal peripheral rim enhancement.

The differential diagnoses of bilateral adrenomegaly are infiltrative disorders such as metastasis from an unknown primary, non-Hodgkin's lymphoma, amyloidosis, sarcoidosis, and neoplasias, such as, bilateral pheochromocytoma, adrenocortical carcinoma and infections like tuberculosis, histoplasmosis, cryptococcosis, coccidiodomycosis and blastomycosis.[2] But, central hypodensity and peripheral rim enhancement of adrenals narrow down the differentials only to tuberculosis and histoplasmosis.[2] Diagnosis of adrenal histoplasmosis can be easily made on FNAC.[7] As adrenal gland is frequently the demonstrable site of active disease, FNAC can suggest the diagnosis which can be further confirmed by culture, polymerase chain reaction (PCR) and urine antigen. These tests can be helpful in differentiating histoplasmosis from tuberculosis.[8] *Histoplasma capsulatum* is an intracellular dimorphic fungus which is commonly seen with in the cytoplasm of the macrophages and exhibit narrow based budding.[9] In FNAC these organisms can also be seen extracellularly as the fragile cytoplasm of the macrophages may get disrupted at the time of making smears. Rapid onsite cytopathological evaluation can suggest immediate diagnosis of infection and hence the treatment can be started at the earliest.[9]

Even in non-endemic regions the possibility of histoplasmosis should always be kept in mind in patients with enlarged, hypoattenuating bilateral adrenal masses with peripheral rim enhancement and enhancing internal septations. Image guided FNAC will demonstrate the disease and should be performed without delay as a great number of patients with adrenal histoplasmosis may develop life-threatening adrenal insufficiency if untreated.

Antifungal agents reduce mortality to less than 25% in patients with disseminated histoplasmosis, where as mortality without treatment can be as high as 80%-100%. Amphotericin B (3 mg/Kg body weight) for 1-2 weeks followed by ltraconazole (200 mg twice daily for at least 12 months) are preferred for patients with severe or moderately severe PDH with liposomal amphotericin B an option in patients with renal dysfunction.[10] Itraconazole (200 mg, twice-daily, for at least 12 months) is considered to be the drug of choice for treatment of patients with less severe illness.[10]

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