Adrenal Histoplasmosis: Unusual Presentations

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Abstract

Background: Histoplasmosis has been sporadically reported from India. Though asymptomatic adrenal involvement has been described in patients with disseminated histoplasmosis; isolated adrenal involvement with adrenal insufficiency (AI) as the presenting manifestation of the disease is rare.

Patients and Methods: We describe 5 immunocompetent men (mean age 55.6 yrs) from a nonendemic area with adrenal histoplasmosis presenting with constitutional symptoms. Three patients had AI at presentation with bilateral adrenal involvement and the other two developed AI during the course of the illness and had unilateral adrenal mass. All the patients had histopathological/cytologically proven adrenal histoplasmosis. ¹⁸FDG-PET done in 3 patients helped in delineating the extent of the disease. Adrenalectomy was done in 2 patients who presented with unilateral adrenal mass. All these patients received Amphotericin B and/or itraconazole treatment which led to symptomatic improvement but AI persisted in all at the end of the follow up of 6 to 18 months.

Conclusion: The diagnosis of adrenal histoplasmosis should be considered in patients presenting with constitutional symptoms and unilateral or bilateral adrenal mass/es with or without AI.

Introduction

Histoplasmosis is a fungal infection caused by Histoplasma capsulatum.¹ Disseminated histoplasmosis is of concern particularly among immunocompromised individuals, alcoholics and at extremes of ages because of the associated high morbidity and mortality.¹ India is considered to be nonendemic area for histoplasmosis. Nevertheless since the first case of histoplasmosis being reported by Panja and Sen (1954) from India,² many cases of disseminated histoplasmosis have been reported mostly from the eastern parts of the country and mostly from eastern part of the country.³ Asymptomatic adrenal involvement has been described in 30-50% of patients with disseminated histoplasmosis.⁴ However, there are very few reports of disseminated histoplasmosis⁵ presenting as unilateral adrenal mass and/or adrenal insufficiency. We describe 5 cases of adrenal histoplasmosis in immunocompetent subjects from nonendemic area who had adrenal insufficiency either at presentation or during follow up from a tertiary care centre of north India.

Subjects, Method and Result

It is a retrospective analysis of five cases of histoplasmosis involving the adrenals admitted in the department of Endocrinology in a tertiary care institute of north India from the year 2007 to 2009. All of them had histopathological evidence of histoplasmosis with adrenal involvement. These cases are illustrated below and summarized in Tables 1 and 2.

Case-1

A 78-years-old male, a retired army personnel, presented with anorexia, weight loss, easy fatigueability and intermittent low grade fever of 2 months duration. On examination, he had body mass index (BMI) of 23.2 kg/m², blood pressure of 130/80 mm Hg without any postural drop. He had no hyperpigmentation, lymphadenopathy or hepatosplenomegaly. On evaluation he was found to have a 4.8*3.4 cm left adrenal mass with necrotic areas and a normal right adrenal (Figure 1). Chest X-ray showed a 1.0 * 1.5 cm calcified nodule in the right lung and mediastinal lymph nodes. Serum electrolytes were normal and hormonal evaluation revealed 0800h serum cortisol of 43 µg/dl (normal 9-19 µg/dl), dehydroepiandrosterone sulphate (DHEAS) 12 ng/ml (normal 500-2500 ng/ml) and 24 hours urinary vanillyl mandelic acid 0.3 mg/d (normal <15mg/day). Serum cortisol after overnight dexamethasone suppression test (ONDST) was suppressible (1.6 µg/dl). HIV serology was nonreactive. Keeping a possibility of adrenocortical carcinoma, he was subjected to adrenalectomy but histopathology of the operated tissue showed extensive necrosis of adrenal parenchyma with dense infiltrate of lymphocytes, giant cells and epithelioid granulomas. In addition there were numerous PAS positive fungi 2-4 micrometer with central dark area and peripheral halo consistent with morphology of histoplasmosis. But he did not receive any antifungal medication from the treating hospital.

After the adrenalectomy, he remained asymptomatic for one and a half year, when he again developed loss of appetite and malaise and presented to our institute. On examination, he was hyper pigmented, afebrile and had significant postural hypotension (20 mm Hg). Systemic examination was non-contributory. Biochemical and hormonal evaluation revealed raised serum potassium (5.6 and 6.0 mEq/L) and low 0800h serum cortisol (2.4 µg/dl). A 250 µg Synacthene (ACTH) stimulation test failed to show an optimal response (serum cortisol 4.3 µg/dl at 30 minutes). Serum DHEAS was low (1ng/dl). On imaging, contrast enhanced computerized tomogram (CECT) abdomen showed bulky right adrenal gland while left adrenal was not visualized. Fine needle aspiration cytology (FNAC) from the right adrenal was non yielding. Fluorodeoxy glucose positron emission tomogram (¹⁸FDG-PET) showed increased uptake in mediastinal lymph nodes, right pulmonary nodule and florid and bright
uptake by the right adrenal gland (Figure 2) suggestive of active and disseminated disease. In view of the above features, a diagnosis of active disseminated histoplasmosis was made. He was started on oral hydrocortisone, fludrocortisone and parenteral liposomal amphotericin-B (3mg/kg body weight for 14 days), followed by oral itraconazole (200 mg twice a day for 12 months). He improved symptomatically and is currently doing well while on therapy.

**Case-2**

A 56-year-old male, farmer by occupation, presented with decreased appetite, recurrent vomiting and weight loss of 2 months duration. He was a chronic smoker with no other co-morbidities. On examination, he was hyperpigmented with significant postural drop in blood pressure. He had no hepatosplenomegaly or lymphadenopathy. Chest X ray revealed widened mediastinum and CECT abdomen revealed enlarged bilateral adrenals with heterogenous enhancement and central attenuation with septations. He had normocytic anemia (hemoglobin 10 gm/dl) and hyperkalemia (serum potassium 5.5-6 meq/l). HIV serology was nonreactive. 0800h serum cortisol was low (5 µg/dl) and 250 µg Synacthene (ACTH) failed to show a response (serum cortisol 5.5 µg/dl at 30 minutes was). Serum ACTH was high (335.5 pg/ml) suggestive of primary adrenal insufficiency. Serum DHEAS was low (79 ng/dl). 18FDG-PET scan revealed intensely increased uptake in both the adrenals and mediastinal lymph nodes. FNAC of the enlarged adrenals revealed histoplasmosis. In view of the progressive disseminated histoplasmosis, patient received parenteral liposomal amphotericin-B (3mg/kg body weight for 14 days), followed by oral itraconazole (200 mg twice a day) along with oral hydrocortisone and fludrocortisone replacement. His condition improved and is currently doing well.

**Case-3**

A 55-year-old forest officer presented with complaints of progressively increasing pigmentation, low grade fever and weight loss of 6 months duration. He was a known case of T2DM. On examination, his BMI was 21 Kg/m², blood pressure of 90/70 mm Hg. On investigation 0800hr serum cortisol was 10.1µg/dl and after stimulation with 250μg ACTH (synacthene), it increased to 13.6 µg /dl. Serum DHEAS was 294 ng/dl. HIV serology was negative.

**Table 1 : The clinical profile of the five patients with adrenal histoplasmosis**

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Age</th>
<th>Sex</th>
<th>Occupation</th>
<th>Lag time (months)</th>
<th>Clinical Presentation</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>Army Personnel</td>
<td>2</td>
<td>Adrenal mass</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>Farmer</td>
<td>2</td>
<td>AI</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>Forest officer</td>
<td>6</td>
<td>PUO</td>
<td>Diabetes</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>M</td>
<td>Laborer</td>
<td>5</td>
<td>Adrenal mass</td>
<td>Alcoholic</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>Farmer</td>
<td>1</td>
<td>AI</td>
<td>Alcoholic palatal ulcer</td>
</tr>
</tbody>
</table>

M=male, F=female, AI=adrenal insufficiency, PUO=pyrexia of unknown origin.

**Table 2 : Clinical profile, Imaging modalities, treatment and follow up of the patients with adrenal histoplasmosis**

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Adrenal insufficiency</th>
<th>Adrenal involvement</th>
<th>FNAC/HP</th>
<th>PET Scan</th>
<th>Treatment</th>
<th>Follow up Duration (yrs)</th>
<th>Clinical improvement</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>Unilateral and later bilateral</td>
<td>Histoplasmosis</td>
<td>High uptake in adrenals</td>
<td>ADR+LA+I</td>
<td>1</td>
<td>+</td>
<td>Persisting</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>Bilateral</td>
<td>Histoplasmosis</td>
<td>High uptake in adrenals</td>
<td>LA+I</td>
<td>0.5</td>
<td>+</td>
<td>Persisting</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>Bilateral</td>
<td>Histoplasmosis</td>
<td>High uptake in adrenals</td>
<td>LA+I</td>
<td>0.5</td>
<td>+</td>
<td>Persisting</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>Unilateral and later bilateral</td>
<td>Histoplasmosis</td>
<td>ND</td>
<td>ADR+I</td>
<td>1.5</td>
<td>+</td>
<td>Persisting</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>Bilateral</td>
<td>Histoplasmosis</td>
<td>ND</td>
<td>I</td>
<td>1.5</td>
<td>+</td>
<td>Persisting</td>
</tr>
</tbody>
</table>

HP=histopathology, ND=not done, ADR= adrenalectomy, LA=liposomal amphotericin, I=itraconazole, AI=adrenal insufficiency
negative. Contrast enhanced CT scan of the abdomen revealed enlarged bilateral adrenals with central necrosis. 18FDG-PET scan showed intense uptake by the enlarged bilateral adrenal glands with no uptake elsewhere. FNAC of the enlarged adrenal revealed histoplasmosis. He received intravenous liposomal amphotericin B followed by oral itraconazole. His condition steadily improved and currently he is well.

Case-4

A 40-year-old male, labourer by occupation presented with left flank pain for 5 months and low grade fever and weight loss for the last 3 months. He was a chronic smoker and alcoholic without any other comorbidities. He had no hyperpigmentation or postural drop in blood pressure and systemic examination revealed no abnormalities except a tender and palpable mass in the left hypochondrium. On investigation, hemogram and serum electrolytes were normal. Serum cortisol at 0800hr was 24.6µg/dl and was non-suppressible after dexamethasone (12µg/dl). The 24 h urinary VMA was normal (2.4 mg). His HIV serology was negative. CECT chest and abdomen revealed small pulmonary nodule in the apico-posterior region of the left lobe and a large (9.5*8.5 cm) left suprarenal heterogenous enhancing mass (Figure 3). FNAC from the mass showed only necrotic material. A possibility of adenocortical carcinoma with sub-clinical hypercortisolism was kept. Patient underwent left adrenalectomy and splenectomy. The excised mass showed extensive necrosis and histopathology was consistent with histoplasmosis (Figures 4, 5). In the immediate postoperative period, he developed adrenal insufficiency and random serum cortisol was 2µg/dl. He was given supplemental hydrocortisone for the same. Subsequently patient received intravenous amphotericin (cumulative dose of 3.5 gm) and itraconazole. Patient is under regular follow up and doing well.

Case-5

A 49-year-old male presented with diffuse abdominal pain, nausea, anorexia and weight loss over 1 month. He was a known case of hypertension for the last 9 years and had been on calcium channel blocker which was stopped one month back due to postural dizziness. He had a non healing ulcer over the hard palate for the past 3 months. He used to smoke and consume alcohol. On clinical examination, he was thin built (BMI-17.2 kg/m2), with buccal pigmentation and had an oval ulcer over the hard palate with irregular edges and granular base. He had significant postural hypotension and rest of systemic examination was unremarkable. On investigations, he had anaemia (Hb 10 gm/dl) and serum creatinine was 2.5mg/dl and serum potassium 4.6 meq/L. HIV serology was negative. Serum cortisol at 0080h was low 10.7µg/dl and after 250 µg Synacthene, it showed a subnormal response (serum cortisol at 30 min, 13.4µg/dl, N 20.3µg/dl). CT abdomen revealed bilateral enlarged adrenals with smooth margins and no calcification. FNAC from the adrenals revealed granulomatous inflammation consistent with histoplasmosis. Biopsy from palatal ulcer showed chronic granulomatous lesion showing intracellular and extracellular fungi consistent with histoplasmosis. He was started on oral itraconazole (200 mg twice a day) for one year and oral hydrocortisone and fludrocortisone replacement therapy. With this treatment he had marked symptomatic improvement with healing of the palatal ulcer. However a repeat CT scan of the abdomen showed persistence of adrenomegaly and a repeat Synacthene test showed poor adrenal reserve at the end of one year. Currently he is on oral hydrocortisone and fludrocortisone and is under regular follow up.

Discussion

We describe five immunocompetent subjects who developed histoplasmosis with adrenal involvement and had adrenal insufficiency either at presentation or during their follow up. Four had disseminated disease and one had isolated adrenal involvement. Treatment with amphotericin and/or itraconazole was rewarding.
Since the first case of histoplasmosis was reported by Panja et al., more cases have been reported sporadically from the eastern parts of India where histoplasma spores had been isolated from the soil of Gangetic delta. Still this fungal infection is largely under-reported possibly due to asymptomatic self limiting course of the mild disease, lack of awareness by treating physician, tuberculosis masquerading as histoplasmosis and lack of proper diagnostic facilities.

Though histoplasmosis have been traditionally thought to be a disease of immunocompromised individuals and occurs at extremes of ages, occurrence of the disease in middle aged immunocompetent hosts as in our study refutes this notion. Similar observations have been made in few other reports from India.

The clinical manifestations of the disease are protean. The spectrum of the disease varies from asymptomatic self limiting disease to progressive disseminated disease involving various organs and usually presents with fever, weight loss and constitutional symptoms. All the patients had severe constitutional symptoms and four had disseminated disease while one had isolated adrenal involvement. Tuberculosis, histoplasmosis and, sometimes sarcoidosis and adrenocortical carcinoma should always be kept in differential diagnosis when an individual presents with fever, weight loss and adrenal mass.

Histoplasmosis presenting as asymptomatic bilateral adrenal enlargement has been described previously but unilateral adrenal involvement is rare. In our study unilateral adrenal mass was seen in two cases at presentation. However, one developed contralateral adrenal involvement at a later stage and the other possibly had subclinical contralateral adrenal involvement to begin with as he developed adrenal insufficiency postoperatively. The unilateral involvement apparently represents early stage of the disease and insidious involvement of other side may occur in due course of time or alternatively both the adrenals might have been involved asymmetrically in the initial stages which may not be evident on imaging as was seen in the above mentioned patients respectively.

Adrenal involvement by histoplasmosis resulting in adrenal insufficiency is an uncommon phenomenon. Kauffman et al. found adrenal involvement in only 12 out of 58 patients with histoplasmosis, and none of them showed clinical evidence of adrenal failure. Similarly in another study 12 patients of bilateral adrenal histoplasmosis were reported in immunocompetent hosts and only three of them presented with adrenal insufficiency. The finding of low incidence of adrenal insufficiency might be due to the fact that disseminated disease brings the patient early and almost 90% of the adrenal tissue is to be destroyed before it manifest as clinical adrenal insufficiency.

The usual CT features of adrenal histoplasmosis include symmetric enlargement with preservation of normal outlines and peripheral enhancement with central hypodense areas. In our series only 3 out of 5 had bilateral adrenal involvement at presentation and 2 developed during the course of illness. Though all our patients had peripheral enhancement with central hypodensity, none had preservation of normal outlines of adrenals, which suggests more advanced disease with significant tissue destruction.

Percutaneous fine-needle aspiration or biopsy either ultrasound or CT guided clinches the diagnosis as was seen in three of our cases. In two patients with unilateral adrenal involvement who underwent adrenalectomy, histopathology of the surgical specimen confirmed the diagnosis of histoplasmosis. The characteristic histopathological examination shows numerous small spherical or oval yeast forms surrounded by a clear ring of space resembling a capsule inside the cytoplasm of histiocytes, hence the misnomer, H. capsulatum as was seen in our case.

The extremely slowly progressive nature of histoplasmosis especially in immunocompetent hosts and nonspecific systemic manifestation of disseminated disease pose a significant dilemma in initiating long courses of relatively toxic antifungal therapy. The functional scintiscans like FDG-PET is useful in determining the activity and extent of the disease and presence of disease, as the trace uptake denotes ongoing infection and inflammation, as was evidenced in three of our patients, where it was performed. So adrenal histoplasmosis is an important differential diagnosis in cases of adrenal masses with intense FDG uptake, even in nonendemic areas.

The recommended treatment is amphotericin B for critically ill hospitalized patients followed by long term oral itraconazole while for relatively stable patients, oral itraconazole alone is effective. The response is quite rewarding as all our patients improved after treatment with anti-fungals. However, adrenal functions usually do not improve after therapy, though there are few reports of normalization of adrenal functions after successful antifungal therapy. None of our patients had recovery of adrenal functions even after 6 to 18 months of follow-up. Recurrence has been described as long as nine years after cessation of treatment, and therefore treatment with antifungals for a duration of one to two years is recommended to reduce the risk of relapse.

In conclusion, adrenal histoplasmosis do occur in immunocompetent hosts from nonendemic areas. The diagnosis should be considered in any patient presenting with unilateral or bilateral adrenal mass with constitutional symptoms. FDG PET may be useful in defining the extent of the disease. Treatment with parenteral and oral antifungals for prolonged duration is rewarding.

References


