



Case report

Disseminated histoplasmosis in India presenting as addisonian crisis with epiglottis involvement

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ABSTRACT

Histoplasmosis is caused by *Histoplasma capsulatum*. Like most fungal infections, histoplasmosis is common in immunocompromised patients. In immunocompetent patient, infection is generally asymptomatic and rarely turns into a disseminated form. Addisonian crisis as presentation of disseminated form has been reported in present. Here, we report a case of disseminated histoplasmosis leading to life threatening adrenal crisis and hypercalcemia in an elderly immunocompetent Indian patient. Appropriate diagnosis and anti fungal and steroid treatment lead to dramatic improvement in patient. Histoplasmosis should be considered in a immunocompetent hosts with adrenal involvement. © 2020 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Histoplasmosis systemic fungal disease with the causative agent is *histoplasma capsulatum* [1]. Like most fungal infections, histoplasmosis is common in immunocompromised patients. In immunocompetent patient, infection is generally asymptomatic and rarely turns into a disseminated form [2]. Histoplasmosis commonly involve lung and respiratory tract mimicking tuberculosis, this lead to delay in diagnosis and treatment which lead to disseminated histoplasmosis involving organs such as the adrenal gland. Asymptomatic adrenal involvement is common but symptomatic adrenal crisis is rare. Here in our case, we report a case of disseminated histoplasmosis presented with adrenal crisis, hypercalcemia and renal failure.

Case report

A male aged 60 years, who was a chronic smoker presented in our emergency department with abdominal pain, oliguria and shortness of breath from last 3 days. He also had history of generalized weakness, back pain, weight loss, reduced appetite, dry cough and change in voice for the last 6 months. He was started on empirical Anti tubercular treatment based on his complaints and x-ray based imaging but no clinical improvement was observed, hence patient stopped treatment after 2 months of therapy. On examination he was conscious, respiratory rate of 30/

min, BP 90/40 mm Hg and pulse 120/min. He had pallor, hoarseness of voice and BMI 17.3 kg/m [2]. Baseline investigations showed hemoglobin 7.3 g/dL, WBC 22000 μ /L (N 90 %, L 10 %), platelets 350,000 μ /L, serum creatinine 2.8 mg/dL, sodium 132 meq/L, potassium 5.5 meq/L, corrected calcium 12.8 mg/dL, Phosphate 1.9 mg/dL, PTH 7.4 pg/mL (low), Vitamin D 1,25 dihydroxyl 32 pmol/L (low), ACE levels normal and ABG showed high anion gap metabolic acidosis. He was treated with IV fluids, ionotropics drug, anti-hypercalcemic measures and hemodialysis.

Keeping in mind his clinical presentation and lab values, a working diagnosis of hypercalcemia of malignancy was considered. His myeloma profile panel was negative and a bone marrow study was unremarkable. Chest x-ray showed bilateral emphysematous changes without any consolidation. Ultrasound abdomen showed mild hepatosplenomegaly with hypoechoic masses in b/l suprarenal glands with normal sized kidneys. 2D echocardiogram showed good LV function with an ejection fraction of 55 %. With above treatment, urine output and breathlessness improved, but blood pressure remained on the lower side and hypercalcemia persisted. Morning & evening cortisol levels were low – 0.5 μ g/dL and 0.6 μ g/dL respectively. Plasma ACTH test was 14.6 pg/mL. Further ACTH stimulation test showed serum cortisol 30 min after 250 μ g synacthen was 1 μ g/dL, which confirmed Addison's disease. Subsequently a non contrast PET scan showed non FDG avid bulky adrenal gland measuring 5.7 \times 2.5 cm (left) and 5.6 \times 2.2 cm (right) (Fig. 1) and fibro-nodular lesion in superior segment of left lobe of lung (Fig. 2). EUS guided fine needle aspiration cytology of the adrenal gland showed budding yeast form of histoplasmosis. Fibre optic laryngoscopy (FOL) was done which showed micro granular appearance of the epiglottis and atrophic cords. The diagnosis of disseminated histoplasmosis leading to

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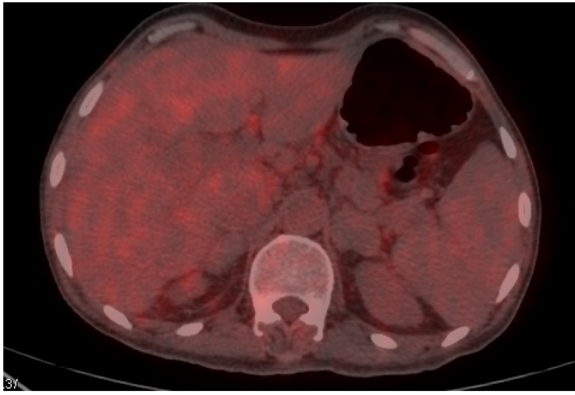


Fig. 1. Non FDG avid bulky adrenal gland measuring 5.7×2.5 cm (left) and 5.6×2.2 cm (right).

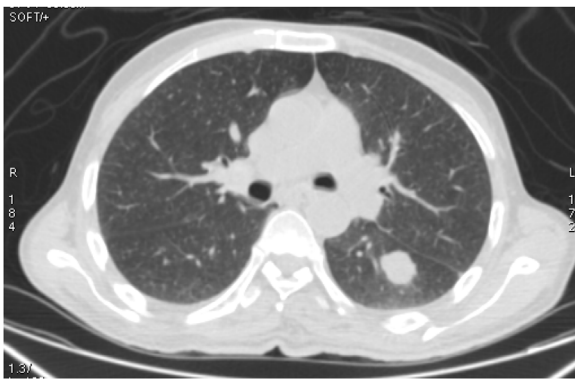


Fig. 2. Fibro-nodular lesion in superior segment of left lobe of lung with emphysematous changes with both lung field.

Addisonian crisis and hypercalcemia was made. To rule of secondary immunodeficiency, a test for HIV negative and CD4, CD8 count were normal. Patient treated with IV liposomal amphotericin B for 2 weeks with steroids followed by oral itraconazole, fludrocortisone and steroids. His serum calcium and creatinine level normalized with treatment. Follow up after 3 months showed symptomatic improvement with weight gain of 10 kg and improvement in voice. Oral itraconazole was continued for 1 year.

Discussion

Histoplasma capsulatum is a dimorphic fungus with a worldwide distribution. Histoplasmosis is endemic in certain geographic area of India including Delhi, Assam, Haryana, Uttar Pradesh and West Bengal [3]. People are infected by inhaling the spores of dimorphic fungus. *Histoplasma* grows on moist soil of caves or river banks which may harbour dropping from birds or bat. It can survive in soil for years and when soil becomes dry, inhalation lead to histoplasmosis infection [4]. The yeast grows within alveolar macrophages initially but later on disseminate to other organs via reticulo-endothelial system. Immunocompetent host disease is self limiting as the immune system confines the infection. Such patient may have mild influenza like symptoms or are asymptomatic. Patient who present with severe symptoms are generally immunocompromised. The spectrum of disease includes pulmonary histoplasmosis to a disseminated form. Dissemination can

involve bone marrow, liver, spleen, adrenal, eyes, brain and gastrointestinal tract [5]. Disseminated histoplasmosis affecting the adrenal gland of immunocompetent adults is rare [6]. Our patient also had lung and probably epiglottis involvement as well. Symptoms can vary in adrenal histoplasmosis depending on involvement of adrenal and residual functioning of adrenal gland. Some patient may have mild adrenal insufficiency such as vomiting, decrease appetite, hyperkalemia, hyponatremia while rarely lead to adrenal crisis [7]. Our patient presented with adrenal crisis, this can be explained as patient was symptomatic for 6 months but due to delay in diagnosis and unable to receive definite treatment lead to worsening of disease course. Eventually when he presented to our department he had adrenal crisis related hypotension and renal failure.

Persistent hypercalcemia was important diagnostic clue in our case. In view of hypercalcemia and low intact PTH, a differential diagnosis of PTH independent hypercalcemia were to consider including malignancy, multiple myeloma and chronic granulomatous disease such as fungal infections, tuberculosis and sarcoidosis. Because in our region tuberculosis is endemic so most patients with clinical features of fever, cough, weight loss receive empirical anti tubercular treatment in primary care centers where the availability of a biopsy is scare. Hypercalcemia in Addison's disease is rare with reported prevalence of 5 % [8]. The pathogenesis of hypercalcemia in hypoadrenalism is complex and incompletely understood. One hypothesis suggests hemoconcentration, hypercitremia and increased affinity of plasma protein for calcium are major causes. Other hypotheses suggest renal tubular reabsorption and increased bone resorption as contributory factors [9]. Improvement of hypercalcemia with steroids proved Addison's disease as the cause for hypercalcemia in our case.

Diagnosis was confirmed on cyto-pathological analysis. Culture remains the gold standard for the diagnosis of histoplasmosis because it allows the isolation and characterization of the fungus; however it requires prolonged incubation, may take up to 8 weeks. Our case was confirmed on cytopathology. The treatment includes oral itraconazole for mild form of disease. As our patient presented with severe disease IV amphotericin B was initially given and maintenance with itraconazole was continued. Long term maintenance up to 1 year is recommended to prevent relapses [10]. Our patient tolerated itraconazole well and had dramatic improvement with therapy.

In summary, with risk of life threatening adrenal insufficiency and availability of effective treatments, adrenal histoplasmosis must be considered even in immunocompetent adults with unexplained hypercalcemia.

Authorship statement

All authors have made substantial contributions to the work reported in manuscript.

Specific Contribution

- 1) Writing of Manuscript: Jatin Agrawal & Anil Arora.
- 2) Drafting of Manuscript: Jatin Agrawal, Naresh Bansal.

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Ethical approval

Not applicable.

Declaration of Competing Interest

None.

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