Case Report

A rare presentation of adrenal histoplasmosis in an immunocompetent patient as an adrenal crisis

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ABSTRACT

A 44-year-old diabetic male presented with hypovolemic shock along with cough-cold, weakness, and low-grade fever for the past 4 months. On laboratory investigation, there were hyponatremia, hyperkalemia, and hypercalcemia. Persistently low parathyroid levels along with a positive adrenocorticotropic hormone stimulation test confirmed primary Addison's disease. On ultrasonography, there was a bilateral adrenal mass over which computed tomography-guided fine needle aspiration cytology was done. Periodic acid Schiff stain of the sample showed intracellular yeast cells resembling histoplasmosis and on culture at 25°C it showed microconidia with successful conversion of mycelium to yeast. The patient was treated with Liposomal Amphotericin B over 2 weeks and steroids, with which the patient gradually improved.

Key words: Addison's disease, Adrenal crisis, Disseminated histoplasmosis

Adrenal histoplasmosis is an uncommon fungal infection of adrenal glands, caused by *Histoplasma capsulatum,* a dimorphic fungus endemic to certain geographical regions, including parts of India, such as Himachal Pradesh [1,2]. This involvement of adrenal glands is particularly significant because it can lead to adrenal crisis, a life-threatening condition, and out of 242 cases reported worldwide, 41.3% of them developed adrenal crisis. Notably, among them, 51 cases were reported only from India [3]. Although it predominantly affects immunocompromised individuals such as those with human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome or those on immunosuppressive therapy; however, lately a rising number of cases have also been reported in immunocompetent individuals [2]. Given that it is important to report this case for facilitation of early suspicion and diagnosis of adrenal histoplasmosis, irrespective of immune status.

CASE REPORT

A 44-year-old diabetic male presented at the casualty department with hypotension, vomiting, abdominal pain, oliguria, hoarseness of voice, and low-grade fever (99–100.2°F) for the last 2 days. In addition, he had a history of back pain, weakness, anorexia, and dry cough for the past 4 months. Furthermore, there was a history of traveling to Himachal Pradesh 2 months ago.

On examination, he was pale and drowsy with a pulse of 118/min, regular rhythm, blood pressure of 90/40 mm of Hg, respiratory rate of 30 breaths/min, and body mass index of 18.5 Kg/m^2.

On laboratory work-up, there was anemia (hemoglobin - 8.2 g%), Leukocytosis (25,000 cells/mm^3) with (75%) neutrophil, raised serum creatinine of 2.8 mg/dL, hyponatremia (122 mEq/L), hyperkalemia (5.5 mEq/L), hypercalcemia (22 mg/dL), low parathyroid (7.4 pg/mL), and vitamin D levels (13 pg/mL) (Table 1). His arterial blood gas (ABG) analysis shows, metabolic acidosis with a high anion gap.

Initially, a provisional diagnosis of hypovolemic shock was made and he was given symptomatic treatment with normal saline at 8 hourly, infusion of noradrenaline started at single strength at 5 mL/h then increased to 10 mL/h, and infusion of zoledronate 4 mg over 15 min single dose to correct hypercalcemia. Along with that injection furosemide, 20 mg was given thrice daily, keeping in mind the hemodynamics of the patient. For correction of metabolic acidosis patient was put up for renal replacement therapy with alternate day hemodialysis and after 3 such sessions,

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Table 1: Hematological and biochemical parameters of the patient

Hematological and Biochemical Parameters	Values	Reference range
Hemoglobin (gm/dL)	8.2	14–17
Total leucocyte count (cells/mm^3)	25,000	4,000–11,000
Platelet count (lakh cells/mm^3)	3.5	1.5–4.5
Creatinine (mg/dL)	2.8	0.6–1.2
Sodium (mEq/L)	122	125–135
Pottasium (mEq/L)	1.9	3.5–4.5
Calcium (mg/dL)	22	8.5–10.2
Phosphate (mg/dL)	7.4	2.5–4.5
Angitensonogen Converting Enzyme (mcg/L)	33	8–52
Parathyroid (pg/mL)	7.4	10–65
Vitamin D3 (pg/mL)	13	30–100
ACTH (pg/mL)	14.6	9–52
Cortisol (mcg/dL) in the morning	0.5	10–20
Cortisol (mcg/dL) in the evening	0.6	3–10

ACTH: Adrenocorticotropic hormone

the patient improved symptomatically with ABG showing a pH of 7.43.

After the patient became hemodynamically stable radiological investigations were performed, chest X-ray PA view showed bilateral emphysematous changes without any consolidation, and ultrasonography of the abdomen showed mild hepatosplenomegaly with hypoechoic mass in bilateral Suprarenal glands with normal-sized kidneys, computed tomography (CT) scan showed bilateral enlargement of adrenal glands with central hypodense areas surrounded by peripheral rim of enhancement, and few calcifications (Fig. 1). His 2D echocardiography showed good left ventricular function with an injection fraction of 55%.

A differential diagnosis, such as hypercalcemia in malignancy was ruled out by normal myeloma profile on serum protein electrophoresis (Total protein-7 g/dL, Albumin- 4.4 g/dL, α-globulin-0.15 g/dL, α-2 globulin-0.8 g/dL, β globulin-1.1 g/dL, γ globulin-1.2 g/dL) and normal bone marrow study as no abnormal cells were found. Sjogren's disease was also ruled out by normal Serum Angiotensinogen Converting Enzyme levels (33 mcg/L) [4]. Based on the initial presentation of hypovolemic shock and bilateral adrenal mass, an adrenal pathology was suspected and a hormonal assay was conducted. Morning and evening cortisol levels were found to be low (0.5 and 0.6 mcg/dL, respectively), along with a normal plasma Adrenocorticotropic hormone (ACTH) level of 14.6 pg/mL. An ACTH stimulation test was done and 30-min cortisol was found to be elevated (250 mcg/dL) Thus, a confirmatory diagnosis of primary Addison's disease was made.

Although his sputum sample was negative for acid-fast bacillus (AFB) in the Ziehl-Neelsen (ZN) stain, the patient was empirically put on first-line anti-tubercular therapy with Isoniazid, rifampicin, pyrazinamide, ethambutol, on suspicion of an adrenocortical tuberculosis (TB) and but patients showed no clinical improvement. Ultimately, CT-guided fine needle aspiration cytology (FNAC) of the adrenal gland was done and

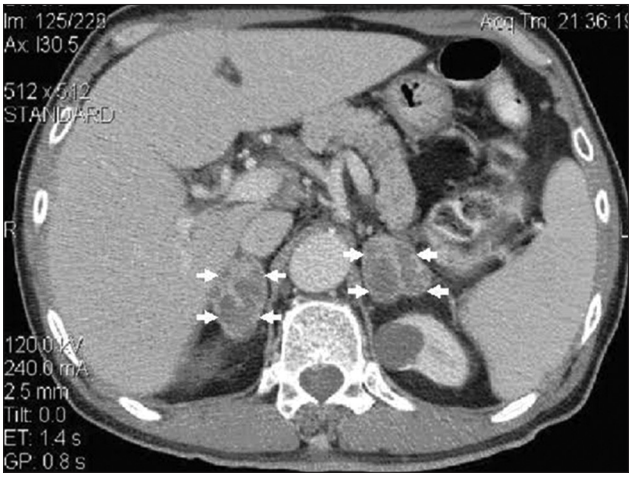

Figure 1: Computed tomography-scan showing bilateral enlargement of adrenal glands with central hypodense areas surrounded by a peripheral rim of enhancement

samples were sent for microbiological examinations. Again, the ZN stain for AFB came negative. Due to the travel history to Himachal Pradesh, a *Histoplasma* endemic zone, on suspicion of underlying fungal pathology, a KOH wet mount was prepared from the sample, which showed tiny yeast cells and thus further Periodic Acid Schiff stain was done. It also showed intra-cellular tiny yeast cells with a "Grape-like appearance" structure having a morphological resemblance to *Histoplasma* (Fig. 2). On tissue culture at 25°C for 1 month, using lactophenol cotton blue stain it showed smooth-walled broadly elliptical, small (2–4 μm) structures, arising on short stalks (microconidia) (Fig. 3). At, 37°C there were yeast cells with mycelium colony formation, showing the dimorphic nature of *Histoplasma* as there was successful conversion of mycelium to yeast.

Thus, a final diagnosis of disseminated histoplasmosis-mediated adrenal crisis was made. Any secondary immunodeficiency was ruled out by negative serology for HIV- 1 and 2 along with normal CD4 and CD8 count (600 cells/mm^3, 200 cells/mm^3, respectively). The patient was put on Liposomal Amphotericin B (5 mg/kg IV daily) for 2 weeks along with intravenous steroids (Injection hydrocortisone 100 mg IV twice daily) followed by which patient was given oral itraconazole (200 mcg thrice daily for 3 days, then 200 mg twice daily for a total treatment duration of 12 months. The patient showed significant clinical and symptomatic improvement and during his follow-up visit after 3 months, there was a weight gain of 2.5 kgs, though oral itraconazole (200 twice daily) was continued for 12 months. Renal function, electrolytes, and liver enzymes were checked on each follow-up visit, every 3 months to rule out any side effects and our patient tolerated oral Itraconazole without any side effects.

DISCUSSION

H. capsulatum is a dimorphic fungus, a neglected tropical disease, with worldwide distribution and endemicity to certain

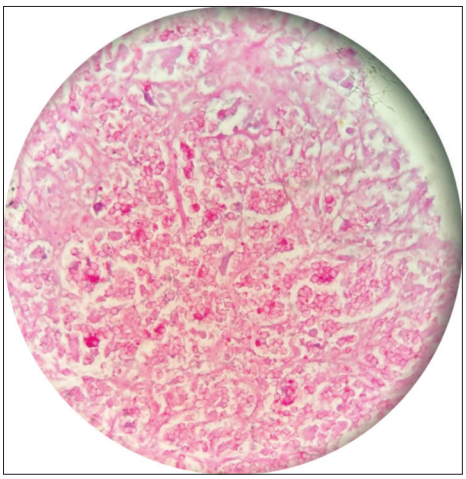

Figure 2: Periodic Acid Schiff stain sowing showed intra-cellular tiny yeast cells with a "Grape-like appearance" structure having a morphological resemblance to *Histoplasma* (Oil immersion, ×100 magnification)

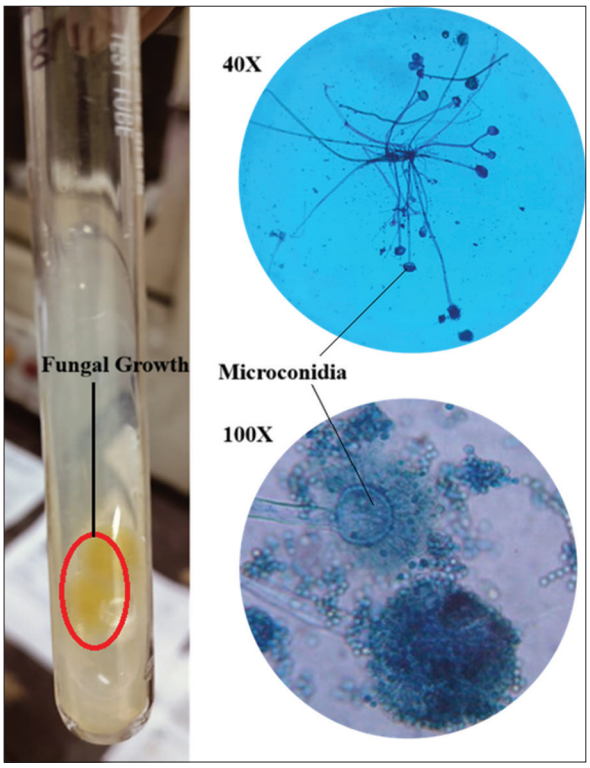

Figure 3: Fungal growth on culture tube & Lactophenol cotton blue (LPCB) stain showing microconidia (40X & 100X magnification)

geographical areas of India, such as Delhi, Assam, Haryana, Uttar Pradesh, and West Bengal [1,2]. When soil becomes dry, the spores become airborne and its inhalation leads to histoplasmosis. Once inside the body, it is converted into yeast form, which initially grows within alveolar macrophages but later on disseminated to other organs through the reticuloendothelial system. In an immunocompetent host, the disease is self-limiting as the immune system confines the infection locally. Such patients may develop mild infection and in most cases are asymptomatic or mildly symptomatic [2]. Individuals who present with severe symptoms are generally immunocompromised [5]. The disease spectrum includes from locally invasive histoplasmosis to disseminated form involving bone marrow, liver, spleen, adrenal glands, eyes, brain, and gastrointestinal tract [6]. Disseminated histoplasmosis, affecting the adrenal glands of an immunocompetent individual is rare but may account for diabetes in our patient [7]. Symptoms in adrenal histoplasmosis can vary depending on the severity of adrenal involvement and residual function of the adrenal glands [8]. Some patients may have mild adrenal insufficiency such as vomiting, anorexia, hyperkalemia, hyponatremia, etc., while rarely it leads to an adrenal crisis [2].

Our patient, having a positive travel history to a histoplasmosis endemic area of Himachal Pradesh, presented with acute adrenal insufficiency and proceeded to adrenal crisis. As India is a TB endemic zone [9] and patients presented with symptoms, such as low-grade fever, weakness, cough-cold, and weight loss, are initially suspected to have TB. This caused a delay in diagnosis and subsequent treatment as our patient also showed non-response to anti-tubercular therapy. Persistently low parathyroid levels and adrenal mass in CT-scan raise the suspicion of adrenal involvement, which was confirmed as primary Addison's disease by ACTH stimulation test [10]. The underlying cause was determined through CT-guided FNAC of the adrenal gland, as microbiological testing of the sample showed growth of *Histoplasma* as stated, culture remains the gold standard for the diagnosis of histoplasmosis, as it allows the isolation, and characterization of fungi. However, it requires prolonged incubation, sometimes up to 8 weeks [11]. There was a case report from Nepal where adrenal histoplasmosis was diagnosed in an immunocompetent individual, who in contrast to our patient, only presented with weight loss but another similar case was reported from Texsus, USA with similar chronic symptoms during the initial period [8,12,13]. There were also other instances where adrenal histoplasmosis was diagnosed incidentally without any acute presentations [14,15]. These varied presentations highlight the need to consider histoplasmosis as a differential diagnosis in the case of adrenal mass presented with or without adrenal crisis. Differential diagnoses considered in our case were primary or metastatic adrenal neoplasms including lymphoma, adrenal hemorrhage, and other disseminated infections, such as TB, all of which were excluded [10,14]. Nonetheless, the survival of the patients before the definite fungal culture report is available remains a major barrier to achieving successful treatment of this disease.

CONCLUSION

Keeping in mind the life-threatening nature of adrenal insufficiency, availability of diagnosis and treatment for adrenal histoplasmosis may be considered even in immunocompetent individuals even though as systemic fungal infection, disseminated histoplasmosis was mostly seen in immunocompromised individuals. However lack of perspective regarding these types of neglected tropical diseases and inclination toward empirical treatment sometimes masked initial symptoms, which delays diagnosis and proper

targeted therapy. Physicians need to be vigilant and keep in mind the differentials, to achieve timely diagnosis and successful recovery.

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