Case Report

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Internal Medicine Section

Out of Site, Out of Mind- A Rare Case of Adrenal Histoplasmosis from a Non Endemic Area

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ABSTRACT

There has been a rising trend in the number of histoplasmosis cases reported in the recent years. However, in southern India, the number of cases is relatively less. This report is about a 46-year-old Indian male from Tamil Nadu who presented with decreased appetite, vomiting, and giddiness. In view of persistent hyponatremia and hypotension, a work-up for adrenal insufficiency was done, and serum cortisol was found to be low. Contrast Enhanced Computed Tomography (CECT) showed bilateral adrenal enlargement with peripheral rim enhancement and hypodense areas within. There was a diagnostic dilemma between tubercular and fungal aetiology. Fine Needle Aspiration Cytology (FNAC) of the adrenal gland showed features suggestive of histoplasmosis. The patient was treated with itraconazole along with steroid replacement therapy, leading to marked improvement in his overall condition. In immunocompetent individuals, disseminated histoplasmosis with adrenal gland involvement is a rare occurrence. As an unusual presentation of histoplasmosis, this case adds to the body of literature available from Tamil Nadu, which is a non endemic region for histoplasmosis, with only 15 cases being reported as of 2018.

Keywords: Adrenal insufficiency, Fungal, Immunocompetent

CASE REPORT

A 46-year-old male presented to the outpatient clinic with history of giddiness, fatigue and loss of weight of five kilograms and loss of appetite for one month. Giddiness was non vertiginous, not associated with syncope, loss of consciousness or vestibular symptoms. He also reported nausea and vomiting for a week. There was no history of any drug intake for the aforementioned weight loss, fever, abdominal pain, headache or diarrhoea. There was no history of tuberculosis or any such contact. He had no co-morbidities. On presentation, the patient was conscious and oriented. His blood pressure was 90/50 mmHg, and pulse rate was 92 beats per minute. General and systemic examination was normal. Thyroid and skin examination was normal. Initial investigations [Table/Fig-1] revealed anaemia (Haemoglobin 9.2 g/dL), deranged renal parameters (urea 80 mg/dL, creatinine 3.13 mg/dL) and hyponatremia (serum sodium 129 mEq/L). Peripheral smear showed normocytic normochromic anaemia with lymphocyte predominance.

Since admission, patient had persistent hypotension with blood pressure 90/50 mmHg. He was given intravenous fluids 0.9% normal saline bolus with maintenance fluids. He continued to have episodes of vomiting and decreased appetite. There was minimal improvement in blood pressure and serum sodium with fluids. In view of persistent hypotension, hyponatremia, hyperkalemia and deranged renal parameters, a diagnosis of adrenal insufficiency was considered. Serum cortisol levels were suppressed - 2.6 (Normal range-3.7-19.4 µg/dL).

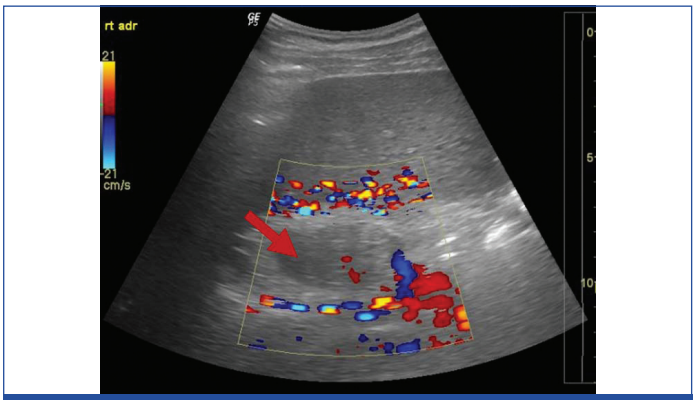
The patient was further worked up to find the aetiology for adrenal insufficiency. Serum Adrenocorticotropic Hormone (ACTH) levels were elevated 71 pg/mL (Normal range-10-60 pg/mL). Ultrasonography of the abdomen showed bilateral bulky adrenals [Table/Fig-2]. CECT of the whole abdomen showed bilateral bulky adrenals (right more than left) with peripheral rim enhancement and hypodense areas within, suggestive of infective aetiology. Few prominent lymph nodes in para-aortic, aortocaval, bilateral inguinal and mesenteric regions were present [Table/Fig-3,4].

Considering an infective aetiology- either tuberculosis or fungal, additional investigations were done. Erythrocyte sedimentation rate was elevated (104 mm at 1 hour). Mantoux test was negative. Chest X-ray and high-resolution CT thorax did not show any lung or hilar lymph node involvement. Transabdominal ultrasound-guided FNAC of the right adrenal gland was then performed. Purulent material was aspirated. Smear of the aspirate showed predominant necrotic background with nuclear debris and occasional clusters of adrenal cells with granular eosinophilic cytoplasm. Few areas show sparse inflammatory infiltrate composed of neutrophils and lymphocytes.

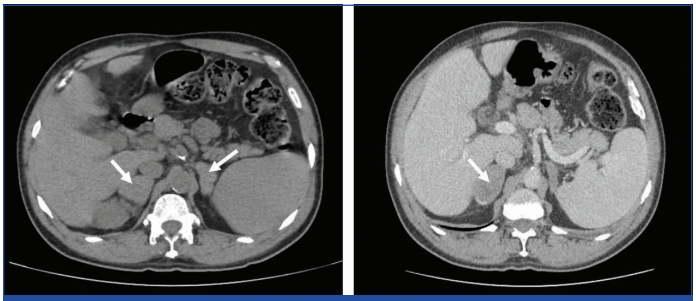
Laboratory parameter	Result	Reference range
Complete blood counts		
White Blood Cells (WBC) (cells/mm^3)	6700	4000-11000
Haemoglobin (g/dL)	9.2	13-17
Mean Corpuscular Volume (MCV) (fL)	97	80-100
Packed Cell Volume (PCV) (%)	27.8	40-50
Platelet count (/mm^3)	320,000	150,000-450,000
Peripheral smear	Normocytic normochromic anaemia with lymphocyte predominance	
Renal function test		
Urea (mg/dL)	80	15-45
Creatinine (mg/dL)	3.13	0.6-1.2
Electrolytes		
Sodium (meq/L)	129	135-145
Potassium (meq/L)	5.3	3.5-4.9
Chloride (meq/L)	91	98-107
Calcium (meq/L)	10	8.7-11
Magnesium (mg/dL)	2.9	2.5-5
Phosphorus (mg/dL)	4.6	1.5-2.5
Urine spot sodium (mEq/L)	59	40-220
Erythrocyte sedimentation rate (mm/hr)	104 mm/hr	0-10
Thyroid profile	FT3-3.05, FT4-1.25, TSH-3.59	2-4.4 pg/mL 0.93-1.7 ng/dL 0.5-5 microIU/mL
HbA1c (gm%)	5.6	<6.5

[Table/Fig-1]: Investigations chart on the day of admission.

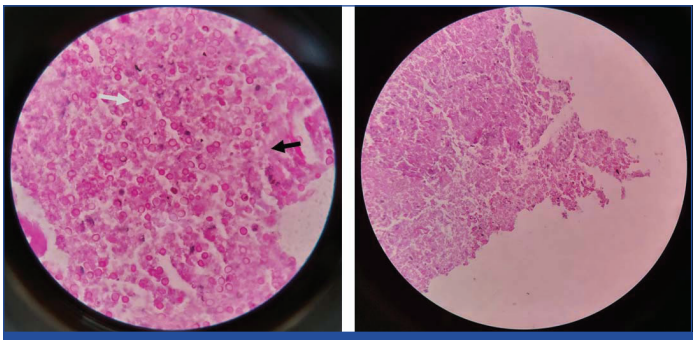
No granulomas, atypical cells or fungal elements seen in the smears studied. Acid fast stain for the aspirate was negative. Cartridge Based Nucleic Acid Amplification Test (CBNAAT) for *Mycobacterium tuberculosis* was negative. Fungal culture of the aspirate was sterile. However, cell block of the aspirate showed necrosis along with numerous fungal elements with morphology suggestive of histoplasmosis [Table/Fig-5,6].



[Table/Fig-2]: Ultrasonography of abdomen showing right bulky adrenal gland (red arrow).



[Table/Fig-3,4]: Plain and Contract-enhanced CT. Abdomen showing bilateral bulky adrenal glands (right > left) (white arrows). (Images from left to right)



[Table/Fig-5,6]: Cell block slides (40X and 10X respectively) showing Periodic Acid-Schiff (PAS) stained cell wall of the fungi (white arrow) in a background of necrosis which appears as a pink amorphous material (black arrow). (Images from left to right)

The patient was started on steroid replacement therapy with oral prednisone 7.5 mg/day and fludrocortisone 0.2 mg/day. His symptoms improved significantly after starting steroid therapy. Acute kidney injury resolved with fluids. Hyponatremia, hyperkalemia and hypotension settled. After the FNAC report, the patient was started on oral Itraconazole 200 mg thrice a day three days followed by 200 mg twice a day. Patient was discharged after two weeks on steroids and antifungal therapy, and was followed-up on outpatient basis after one week and monthly thereafter. On follow-up, there was marked clinical improvement and patient was advised to continue itraconazole and steroids for 12 months. He was counseled regarding the possible side-effects of steroids, none of which were noted on follow-up.

DISCUSSION

The presentation of adrenal insufficiency varies from mild non specific symptoms to life threatening shock, and a high index of suspicion is required [1]. Adrenal insufficiency can be classified into primary, secondary and tertiary. Primary adrenal insufficiency is mainly caused due an adrenal gland pathology causing decreased glucocorticoid and aldosterone production. It has a prevalence of 82-144 per million and incidence of 4.7-6.2 per million in Caucasian populations [2].

In India, the incidence and prevalence is however much lower, with no specific data available [3]. Primary adrenal insufficiency can be caused due to an autoimmune aetiology, congenital mutations, drugs, adrenal haemorrhage, adrenal infiltrations or infections. In the western world, the most common cause is autoimmune adrenalitis [2]. In developing countries including India, bilateral adrenalitis is most commonly due to an infective aetiology, with tuberculosis being a common cause [4]. Other infective causes include fungal (histoplasmosis) and viral {Human Immunodefiency Virus (HIV) and Cytomegalo Virus (CMV)} [2]. Secondary adrenal insufficiency refers to pituitary disorders leading to inadequate secretion of corticotropin and chief causes include pituitary tumours, apoplexy and hypophysitis. Tertiary adrenal insufficiency refers to disorders causing impairment of corticotropin releasing hormone by the hypothalamus, mostly seen in patients after abrupt cessation of high dose steroids.

In this patient, as imaging showed bilateral adrenal enlargement and FNAC of adrenal gland revealed necrosis, there was a diagnostic dilemma between tuberculosis and fungal infection as the infective aetiology. With tuberculosis being the most common infective aetiology in India and Mantoux test being negative in this patient, it was challenging to consider a possibility of a fungal aetiology in a non endemic region. However, the diagnosis was clinched by the FNAC cell block showing fungal elements and features suggestive of histoplasmosis.

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus with world-wide distribution. It occurs by the inhalation of spores of the fungus. *Histoplasma* grows on moist soil of river banks or caves which mainly harbor bat droppings. These spores can survive for many years in soil and when this soil gets dry, inhalation of these infectious microconidia leads to infection [5].

Globally, over half a million people get infected with *Histoplasma* infection, with an average of 100,000 people developing disseminated disease [6]. However, it is not commonly reported in the Indian literature. In India as of 2018, only 388 cases of histoplasmosis have been reported out of which, 15 cases have been reported from the state of Tamil Nadu [7]. It has been documented in the soil of the Gangetic plains. It is endemic in states such as West Bengal, Assam, Haryana, Delhi and Uttar Pradesh but very rare in south Indian states like Tamil Nadu [5].

Patients with an immunocompromised state are more prone for fungal infections like histoplasmosis. Although uncommon, immunocompetent patients are also occasionally infected with no reported gender predilection. In immunocompetent hosts, most infections (50-90%) result in self-limiting flulike symptoms [8].

Histoplasmosis has three major clinical presentations-pulmonary, progressive disseminated, and cutaneous histoplasmosis. Of the three, pulmonary histoplasmosis is the most common form which presents with mild self-limiting disease. Progressive disseminated form is rare and presents as chronic disease in immunocompetent individuals or acute progressive disease in immunosuppressed hosts [9]. It may affect the lungs, gastrointestinal tract, reticuloendothelial system, bone marrow, and the adrenal glands. The adrenals are commonly affected via haematogenous route in immunocompromised patients. However, cases have been reported where adrenal histoplasmosis occurs in otherwise immunocompetent hosts in India and other countries as well. In India, as of 2019, 33 cases of adrenal histoplasmosis have been reported [9]. In a study of 61 immunocompetent individuals,

adrenals were the most affected organ seen in 55% of studied patients [10]. Adrenal gland serves as the only site of active fungal disease in such patients. However, isolated bilateral adrenal gland involvement is rare without involvement of other systems [11].

In this patient, disseminated histoplasmosis involved bilateral adrenal glands as well as the abdominal lymph nodes in an immunocompetent individual. The common differentials for adrenal histoplasmosis include tuberculosis, primary adrenal malignancy, adrenal blastomycosis or coccidioidomycosis. In a country like India where tuberculosis is endemic, it is often misdiagnosed as tuberculosis and the patient is empirically started on antitubercular therapy [9].

Apart from fungal culture and cytology, other methods of confirming a diagnosis of histoplasmosis include antigen testing in urine and serum, antibody testing and polymerase chain reaction [12]. In this patient, these could not be done due to unavailability of these tests in our set-up. Bone marrow aspiration and biopsy with fungal culture can be performed in patient with pancytopenia, which was not done in this patient as his cell lines were normal. Culture remains the gold standard for diagnosis, however, the sensitivity varies based on clinical manifestations (42% in pulmonary disease versus 74% in disseminated disease) [13]. This patient's culture was sterile, and the diagnosis was based on histopathological, radiological and clinical correlation. This reliance on histopathology for diagnosis in the absence of growth in fungal culture has been noted in other studies [14].

As recommended by the Infectious Disease Society of America (IDSA), treatment for disseminated histoplasmosis includes an induction phase to achieve clinical remission and a maintenance phase to prevent relapse. Moderate to severe cases are treated with Inj. Liposomal Amphotericin B 1 mg/kg/day, a parenteral antifungal agent for induction phase followed by oral itraconazole for maintenance phase. Mild cases can be treated directly with oral itraconazole 200 mg/day [15]. As this patient was stable with limited disease, he was treated with oral itraconazole upfront, with which he showed clinical improvement after one week of starting therapy.

CONCLUSION(S)

Disseminated histoplasmosis with adrenal gland involvement in a non endemic area especially in immunocompetent individuals is a rare occurrence. It is important to consider adrenal insufficiency in patients presenting with chronic fatigue in combination with unexplained hypotension, hyponatremia and hyperkalemia.

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