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Disseminated histoplasmosis presenting as adrenal insufficiency: A case report

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ABSTRACT

This report aims to highlight rarity of disseminated histoplasmosis (DH) presenting as adrenal insufficiency and the need for considering it in the differential diagnosis, even in non-endemic areas. A case is presented of a 69-year-old male patient with a background of hypertension and diabetes mellitus, with a persistent fever, significant loss of weight, and general weakness. Imaging studies showed adrenal masses in both adrenal glands, and laboratory tests showed hyperkalemia and hyponatremia. Hormonal tests confirmed the diagnosis of adrenal insufficiency. CT-guided adrenal biopsy confirmed the diagnosis of histoplasmosis. The patient received a 14-day course of Amphotericin B, followed by oral Itraconazole and glucocorticoid substitution therapy, with improvement in adrenal function over a period of time.

1. Introduction

Histoplasma capsulatum is a dimorphic fungus that causes histoplasmosis, which can progress to disseminated histoplasmosis (DH)—a rare but potentially life-threatening systemic fungal infection. This pathogen is endemic to certain regions, particularly in the Ohio and Mississippi River valleys in the United States, as well as parts of Central and South America, Africa, and Asia [1].

Most people who inhale *Histoplasma capsulatum* spores have no symptoms or mild flu-like illness that resolves on its own. The clinical presentations of histoplasmosis depend on the age, underlying diseases of the patient, and most important, the immunologic status of the host, as well as the size of the inoculum inhaled [2]. The clinical spectrum of histoplasmosis is highly diverse, encompassing variations in disease cadence (acute, subacute, and chronic), onset (primary or reactivation), distribution (pulmonary, mediastinal, disseminated, or isolated extrapulmonary), and severity (asymptomatic, mild, or moderate-severe). This broad range of clinical presentations often leads to delays in diagnosis.

Patients with immunocompromised conditions are at greater risk of developing progressive disseminated histoplasmosis (PDH), a severe form of histoplasmosis that spreads to various extrapulmonary organs, particularly the liver, spleen, gastrointestinal tract, and bone marrow [3,4]. However, it can occasionally present in immunocompetent hosts, making it a diagnostic challenge [4,5]. The infection is more common in tropical and subtropical regions; however, in countries like Bangladesh, disseminated histoplasmosis remains under-recognized.

However, in non-endemic areas, adrenal histoplasmosis is often mistaken for other diseases with similar clinical and radiological findings, such as tuberculosis, which is far more common in many parts of the world. An overlap in such a clinical presentation and imaging characteristics underlines the importance of broad differential diagnosis and emphasizes the need for thorough diagnostic evaluation to establish the correct etiology of adrenal masses. This is further complicated because *Histoplasma* infection may cause systemic symptoms indistinguishable from many other chronic infections and malignancies; confirmation of diagnosis and treatment therefore requires a combination of clinical, imaging, and invasive diagnostic techniques.

In tuberculosis-endemic regions, such as Bangladesh, granulomatous diseases are often treated empirically as tuberculosis (TB) due to its high prevalence. However, failure to respond to anti-tubercular therapy

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should prompt clinicians to consider alternative diagnoses, including fungal infections like histoplasmosis. In particular, disseminated fungal infections can mimic the clinical presentation of tuberculosis, posing diagnostic challenges, especially in patients with comorbidities such as diabetes mellitus.

The aim of this case report is to highlight a rare but potentially life-threatening cause of adrenal insufficiency (AI) due to disseminated histoplasmosis, emphasizing the diagnostic challenges in regions like Bangladesh, where tuberculosis is more prevalent. It aims to raise awareness about the growing incidence of histoplasmosis in non-endemic areas, encourage timely diagnosis, and stress the importance of considering this condition in the differential diagnosis of AI, even in immunocompetent individuals.

2. Case presentation

A 69-year-old male presented to a tertiary care hospital with a 2-month history of persistent low-grade fever, progressive weight loss of approximately 9 kg, anorexia, and generalized weakness (day 0). He reported no gastrointestinal disturbances, cough, dyspnea, or night sweats, and had no recent history of travel or exposure to infectious agents. His past medical history included type 2 diabetes mellitus, diagnosed 22 years ago and poorly controlled (HbA1c 9.9 %), for which he was on oral hypoglycemic agents, as well as hypertension, managed with olmesartan. On physical examination, he appeared cachectic and malnourished, with vital signs showing a temperature of 101 °F, blood pressure of 140/80 mmHg lying down and 130/70 mmHg standing, a pulse of 84 bpm, and normal respiratory rate. No signs of

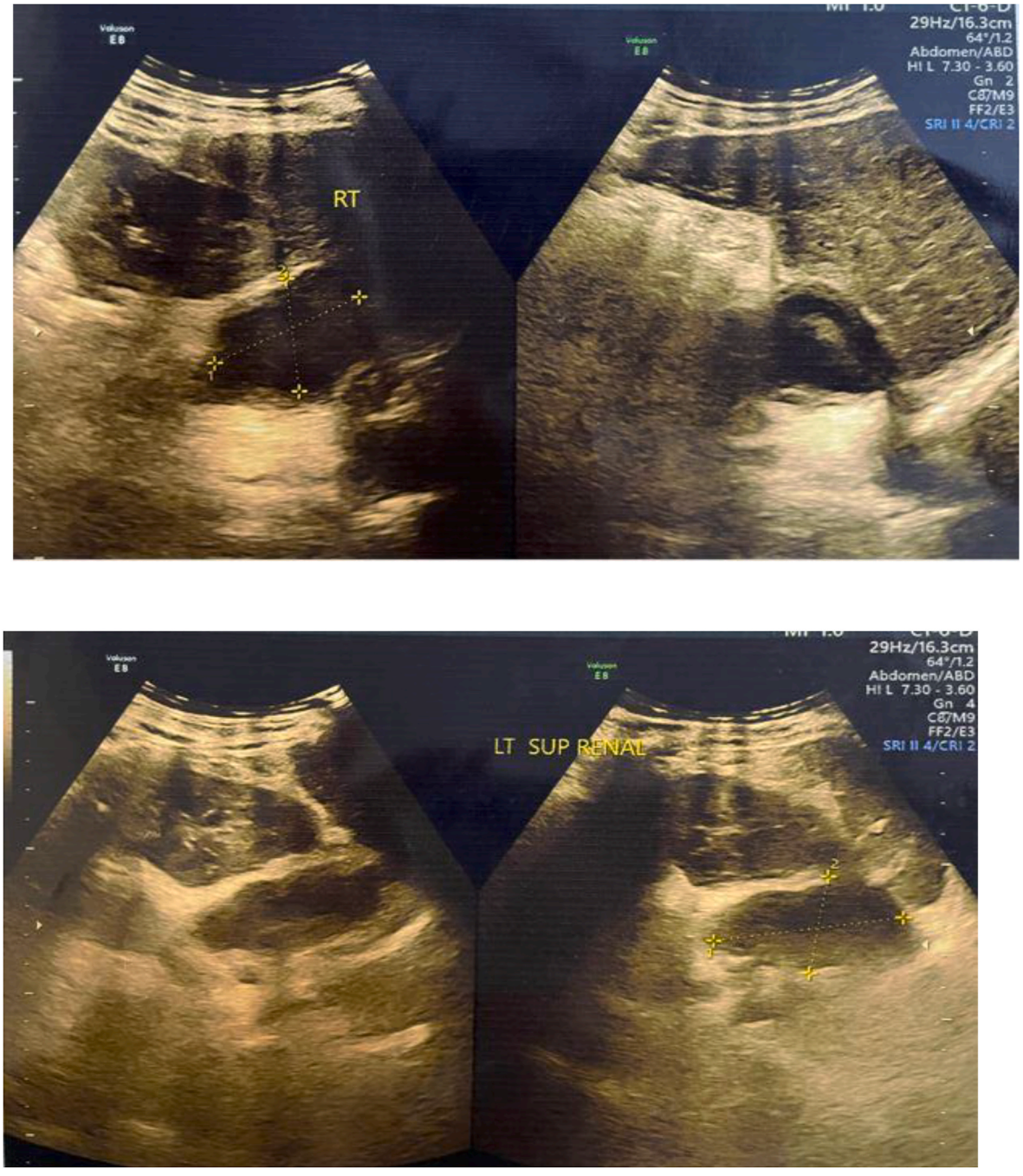

Fig. 1. Ultrasonogram showing bilateral adrenal mass.

lymphadenopathy, anemia, or other systemic abnormalities were observed.

Initial laboratory investigations revealed a hemoglobin level of 12.8 g/dL, mild hyponatremia (sodium 129.7 mmol/L), and an elevated ESR of 65 mm at first hour. Urinalysis showed significant glycosuria without ketonuria, and imaging studies, including an abdominal ultrasound and CT scan, identified bilateral adrenal masses (right: 4.2 × 2.4 cm, left: 3.8 × 2.5 cm) (Fig. 1). Given the imaging findings of bilateral adrenal masses and the clinical picture of fever and weight loss, a provisional diagnosis of adrenal tuberculosis was made, considering the high prevalence of tuberculosis in the region. Hormonal studies to assess adrenal function were within normal limits, with a 9 a.m. serum cortisol level of 19.8 mcg/dL and an adrenocorticotropic hormone (ACTH) level of 10.62 pg/mL. A CT-guided fine-needle aspiration cytology (FNAC) of the adrenal mass was suggested but the patient declined. A trial of antitubercular therapy (ATT) was initiated empirically (day 4).

However, the patient did not respond to ATT, and his condition continued to deteriorate over the next 2 months, prompting a re-evaluation of the diagnosis (day 76). He developed recurrent vomiting, fatigue, and weakness, ultimately requiring readmission to the hospital. Upon examination, he was found to be confused, with a Glasgow Coma Scale (GCS) score of E4 M6 V2. His pulse was 110 beats per minute and of low volume, while his systolic blood pressure was 74 mmHg. His oxygen saturation was 98 % on room air, and his chest was clear. He was resuscitated with bolus intravenous fluid along with other supportive measures. Blood samples were sent for relevant investigations, which revealed notable hyponatremia and hyperkalemia. The 9 a.m. serum cortisol level was 19.9 μg/dL, falling within the normal range; however, the adrenocorticotropic hormone (ACTH) level was 124 pg/mL, indicating adrenal insufficiency. As a result, hydrocortisone injection was added to the ongoing management plan.

After initial stabilization, the patient underwent specialized investigations, including a CT-guided tru-cut biopsy of the right adrenal mass (day 86). Histopathological examination revealed intracellular yeast-like organisms, with positive staining for Periodic acid–Schiff (PAS) and Gomori methenamine silver (GMS). Fungal culture on Sabouraud's dextrose agar, incubated at room temperature, revealed growth of a dimorphic fungus suggestive of Histoplasma capsulatum after three weeks, confirming the diagnosis of adrenal histoplasmosis (day 107). Additional tests, including a bone marrow study, showed focal ill-defined histiocytic aggregates suggestive of granulomatous infections, and a urine *Histoplasma* antigen test returned highly positive, indicating disseminated histoplasmosis. However, culture from the bone marrow aspiration was not performed due to resource limitations.

The patient was started (day 88) on intravenous Amphotericin B deoxycholate (1 mg/kg/day) for 14 days, followed by oral Itraconazole (400 mg/day in divided doses). Over the following weeks, his symptoms improved significantly, with resolution of fever, weight gain, and regained strength. The patient attended follow-up visits every 3 months, and his condition remained stable, with no recurrence of symptoms or adrenal insufficiency.

Subsequent evaluation of the patient after 11 months of treatment indicated significant improvement in adrenal function. The morning cortisol level increased to 18 μg/dL at 9 a.m., which is within the normal range. The ACTH stimulation test showed a baseline cortisol level of 14 μg/dL, rising to 25 μg/dL after 30 minutes. Additionally, plasma ACTH normalized at 30 pg/mL, indicating an intact hypothalamic-pituitary-adrenal axis. The patient had normal electrolytes with sodium and potassium levels within normal range. Steroid replacement was then tapered off gradually, while Itraconazole was continued for a total of 12 months.

3. Discussion

Histoplasmosis typically presents as a self-limiting pulmonary infection in immunocompetent individuals but can disseminate through the reticuloendothelial system in those with impaired cellular immunity, as seen in patients with poorly controlled diabetes mellitus, HIV, or those on prolonged immunosuppressive therapy. It can involve the adrenal gland in several ways like extensive destruction of the adrenal cortex, extracapsular perivasculitis and granulomatous inflammation [6].

DH frequently involves the adrenal gland (80 %) and presents as adrenal enlargement but does not always cause AI [6,7]. A literature review from 1971 to 2012 reported up to 41.3 % of patients with adrenal histoplasmosis develop AI [8]. AI usually is a result of extensive destruction of both the adrenal glands by infection. Chronic infection can also lead to atrophy and calcification, leading to a higher risk of development of AI [9,10].

AI classically manifest as fatigue, weight loss, anorexia, dizziness, weakness, salt craving, abdominal pain, orthostatic hypotension, etc. The nonspecific nature of these symptoms can cause a delay in diagnosis, increasing the risk of a life-threatening adrenal crisis. It can present as an acute deterioration in health status associated with hypotension and usually with a postural drop of blood pressure. Unless it is promptly diagnosed and treated with IV fluid and glucocorticoids replacement outcome is fatal. As our patient was not a case of HIV/AIDS or not on any immunosuppressive therapies, a diagnostic delay was occurred. Diagnosis is further challenged when serum cortisol and ACTH reports were within normal range during initial workup. But, presence of suggestive clinical features along with persistent hyponatremia and a normal-to-high potassium level gave a clue to underlying adrenal insufficiency. Subsequent presentation with acute adrenal crisis eventually unveiled underlying PAI. Imaging, such as a CT scan, typically reveals bilateral adrenal masses with peripheral enhancement and central hypodensity, which can mimic other conditions like adrenal neoplasms, tuberculosis, or other fungal infections such as cryptococcosis and coccidioidomycosis [11,12].

The patient required continued glucocorticoid replacement along with antifungal therapy for disseminated histoplasmosis infection, consistent with the natural history that has described in cases of AI due to histoplasmosis. Our patient did not require mineralocorticoid replacement probably due to sufficient residual adrenal reserve he had to sustain aldosterone synthesis, unlike the majority of AI patients who have deficits in both glucocorticoids and mineralocorticoids. Therefore, among individuals with disseminated histoplasmosis infection, the extent of adrenal damage and speed of recovery even after successful antifungal therapy varies greatly [13,14]. Interestingly, Patients with disseminated histoplasmosis are at increased risk of developing adrenal insufficiency (AI) even if they initially have normal adrenal function. Recovery following appropriate antifungal therapy is also not universal rule [15]. It is important to recognize that adrenal recovery may be incomplete, and some patients may continue to require lifelong steroid replacement. It is thus crucial to alert the patient and as well as treating physician about this varied presentation of AI in a case of disseminated histoplasmosis to avoid future adrenal crisis.

While *histoplasmosis* is not widely recognized in Bangladesh, evidence suggests it is underreported rather than absent. Histoplasmin skin tests in the 1960s–70s showed 12–23 % positivity, indicating prior exposure [16,17]. Since the first documented case in 1982, several cases, mostly disseminated, have been reported in both immunocompromised and immunocompetent individuals [18,19].

Besides, Bangladesh shares the Indo-Gangetic plain with regions in India where *histoplasmosis* is endemic. The presence of *Histoplasma capsulatum* in soil suggests potential local transmission. Many cases may be misdiagnosed as tuberculosis, given similar clinical features or underreported. Our patient had no travel history or clear exposure, supporting the likelihood of indigenous acquisition. Increased awareness and improved diagnostics are crucial to understanding the true burden of histoplasmosis in Bangladesh.

This case reinforces the importance of considering disseminated histoplasmosis in the differential diagnosis of adrenal insufficiency,

especially in regions where fungal diseases may be more common and often underdiagnosed or underreported. Early recognition and prompt initiation of antifungal treatment, coupled with adrenal support, are crucial in enhancing outcomes in patients.

CRediT authorship contribution statement

Md. Asaduzzaman: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Data curation, Conceptualization. **Ranjon Kumer Roy:** Writing – review & editing, Supervision, Resources, Project administration, Data curation, Conceptualization. **Suchanda Roy:** Writing – review & editing, Validation, Resources. **Nasad Ahmed:** Writing – original draft, Data curation, Conceptualization. **Sazeda Akter:** Writing – original draft, Project administration, Data curation. **Monotush Ronjon Chando:** Writing – review & editing, Supervision, Resources, Project administration.

Consent

Written informed consent was obtained from the patient's father for publication of this case report and the accompanying image. A copy of the written consent is available for review by the Editor-in-Chief upon request.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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