CASE REPORT

Infectious causes of Addison's disease: 1 organ—2 organisms!

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BACKGROUND

Infectious aetiologies are the most common causes of primary adrenal failure (Addison's disease) in low/middle-income countries while in the western world autoimmune causes predominate. The infections attributed to cause Addison's include disseminated gonococcal infection, tuberculosis, histoplasmosis, cryptococcosis and cytomegalovirus (CMV) infection. Here, we describe two classical cases of Addison's due to infections of the adrenal gland.

CASE PRESENTATION

Case 1

A 55-year-old woman from North India was admitted with history of multiple episodes of vomiting. She had history of severe loss of appetite and loss of weight. There was also history of increased body pigmentation for the last 6 months. At admission, she was drowsy with tachycardia of 116 beats per minute and her blood pressure was 80/50 mm Hg in supine position associated with a significant postural drop. There was hyperpigmentation of fingers, face, oral mucosa and flexures. The rest of the system examination did not reveal any significant clinical finding. Initial biochemical parameters showed serum sodium of 116 meq/L and serum potassium of 6.1 meq/L. Arterial blood gas analysis showed pH 7.2 and bicarbonate 14.9 mEq/L. A diagnosis of acute adrenal insufficiency was made, and after drawing blood sample for cortisol and adrenocorticotropic hormone (ACTH), she was given a 100 mg bolus dose of intravenous hydrocortisone and 2 L of 0.9% saline. Investigations showed serum cortisol of 39.02 nmol/L (171–536) and elevated ACTH of 818.8 pg/mL (5–60) confirming diagnosis of primary adrenal insufficiency. With initial management, her blood pressure improved and steroids were tapered to oral hydrocortisone (25 mg/day) with oral fludrocortisone 0.1 mg once a day. Contrast-enhanced CT (CECT) of the abdomen revealed bilateral symmetrical enlarged adrenals with preservation of contour without any calcifications (figure 1A). The rest of her hormone profiles were within normal limits ruling out a polyendocrinopathy syndrome. Antinuclear antibody immunofluorescence (ANA-IF) and retroviral serology were negative. CT-guided biopsy from enlarged adrenal glands was performed which revealed dense lymphoplasmacytic cell infiltrates with collection of epithelioid cells forming

granuloma (figure 1B–E). There were no giant cells and stain for acid-fast bacilli was negative. Chest X-ray was normal and Mantoux test showed induration of 20 mm (strongly positive).

CASE 2

A 52-year-old woman from north India presented to the medicine outpatient department with history of fever, fatigue and occasional episodes of vomiting of 6 months' duration. On examination, she was pale with a blood pressure of 96/60 mm Hg associated with a postural drop to 72/50 mm in erect posture. There were no other significant clinical signs. Investigations revealed anaemia with haemoglobin of 8.6 g/dL, elevated erythrocyte sedimentation rate (ESR (68 mm/hour), hyperkalaemia (serum potassium of 5.9 meq/L) and hyponatraemia (serum sodium of 122 meq/L). Abdominal ultrasound performed showed bilateral bulky adrenals. CECT abdomen confirmed bilateral symmetrical enlargement of adrenals with preserved adrenal contours (figure 2A). Her hormone profile showed decreased serum cortisol levels of 61.2 nmol/L (171–536) with elevated serum ACTH of 688 pg/mL (5–60). The rest of the hormones evaluated, that is, thyroid, oestrogen, progesterone, luteinising hormone, follicle-stimulating hormone and prolactin, were in normal range. ANA-IF and HIV serology were negative. She was started on oral hydrocortisone in divided doses (10 mg-5 mg-5 mg) for adrenal insufficiency. She was taken up for ultrasound-guided adrenal biopsy for aetiology of her adrenal failure. Biopsy showed tissues with predominant necrosis and inflammatory cells. There were scattered histiocytes along with intracellular with prominent extracellular fungal spores, suggestive of *Histoplasma* species (figure 2B–E). CECT of the head was normal.

OUTCOME AND FOLLOW-UP

Case 1

With a biopsy picture consistent with adrenal tuberculosis, the patient was started on antituberculous therapy of daily weight-based 4-drug regimen. The patient improved symptomatically and was discharged on oral hydrocortisone and fludrocortisone. Two months into the treatment, she is currently asymptomatic and is well compliant to antituberculous therapy with steroid supplementation and was started on continuation phase of antituberculous therapy with isoniazid and rifampin with normalisation of electrolytes and hyperpigmentation.

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Figure 1 (A) Contrast-enhanced CT imaging of the abdomen showing enlarged adrenals (arrow heads). (B) Biopsy specimen showing a core biopsy with <5% area showing necrosis (H&E; 40x). (C) Biopsy specimen core showing junction between the necrotic and the viable area (H&E; 200x). (D) Viable area of the core biopsy specimen showing dense lymphoplasmacytic cell infiltrate along with vague epithelioid cell granulomas (H&E; 400x). (E) Acid-fast bacilli (AFB) stain of the core biopsy specimen negative for any AFB positive bacilli.

Case 2

Since there was no other focus on the CT of the chest, abdomen or brain, a diagnosis of primary adrenal histoplasmosis causing adrenal insufficiency was made. Oral itraconazole 200 mg two times per day was added and steroids were continued. Patient's symptoms improved, and 3 months later, she is doing well with steroids (oral hydrocortisone 20 mg/day with oral fludrocortisone 0.1 mg once a day) and normalisation of serum electrolytes.

DISCUSSION

The first case of adrenal failure was reported by Sir Thomas Addison in 1855.¹ The aetiology of adrenal insufficiency varies in different geographical areas. Data from developed countries show that autoimmune causes account for 70%–90% of hypoadrenalism cases.^{2,3} However, in developing and underdeveloped nations, 39%–51% of Addison's disease are due to infective pathology.^{4,5} Infections including tuberculosis, histoplasmosis, cryptococcosis, paracoccidioidomycosis and CMV infection have been described to cause adrenal failure. Adrenal insufficiency is seen in at least 17% of patients admitted with HIV infection.⁶ CMV, *Mycobacterium tuberculosis*, *Mycobacterium avium-intercellulare*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis jiroveci*, *Toxoplasma gondii*, Kaposi's

Figure 2 (A) Contrast-enhanced CT imaging of the abdomen showing: bilateral enlarged adrenals with preserved contours (arrow heads). (B) Multiple core biopsies with more than 90% of the area showing necrosis (H&E; 40x). (C) Viable areas of the core biopsy specimen showing dense macrophage infiltrate (H&E; 200x). (D) The necrotic area of core biopsy under oil immersion showing plenty of nuclear debris and negative shadows of fungal profiles (black arrows) (H&E; 400x). (E) Periodic acid-Schiff (PAS) stain in the core biopsy demonstrating both intracellular as well as extracellular 3–4 µm round to oval budding yeast forms of *Histoplasma* (yellow arrows). The inset shows a macrophage loaded with *Histoplasma* (PAS; 1000x).

sarcoma, lymphoma and bilateral adrenal haemorrhage are the usual causes of adrenal failure in patients with HIV infection. Due to its high prevalence, features of adrenal insufficiency should be actively looked for in patients with AIDS.⁶

Tuberculosis is thought to be the causative agent in 47% of cases of adrenal failure in India.⁵ In most cases of adrenal tuberculosis, concomitant pulmonary or other organ involvement is seen. Isolated adrenal tuberculosis is a rare manifestation and accounts for only 1%–2% of adrenal incidentalomas. Isolated involvement is thought to occur due to the resolution of the primary pulmonary foci by the patient's immunity while the disseminated lesion might escape the immune process.⁷ Patients may present de novo with acute adrenal crisis or may present with a slowly progressive, subacute adrenal failure. Most common imaging features (60% cases) are bilaterally enlarged adrenal. Adrenal glands preserve their contour in 50% of cases.⁸ In a retrospective study on causes of bilateral enlargement of adrenals from India, tuberculosis was found to be accounting for 27% of cases and was the most common infective cause.⁹ A definitive diagnosis can only be made by histopathology, either on fine-needle aspiration (FNA) or image-guided biopsy. Treatment with antituberculous therapy is usually curative but the damage to the adrenal gland may be permanent warranting life-long steroid supplementation.

Histoplasma capsulatum is a dimorphic fungus which has high propensity to affect the adrenal gland. Lungs are often the primary site of infection. Risk factors include HIV infection with CD4+ T cell count below 150/µL, exposure to chicken coops and presence of diabetes mellitus. There is a geographical clustering of the infection worldwide. For example, the Gangetic basin and Northeastern India are endemic to the fungus while Central and North America, especially along Ohio and Mississippi rivers, have high prevalence of histoplasmosis.^{10,11} Various cases were sporadically reported from Eastern and Northern India since the first report of an adrenal histoplasmosis case in 1954.^{12–14} Fever of unknown origin is the most common presenting symptom in disseminated disease. Even though imaging frequently shows adrenal enlargement, adrenal failure is a rare phenomenon in *Histoplasma* when compared with the other infectious aetiologies. A series of five cases from North India suggested the usefulness of ¹⁸fluorodeoxy-glucose positron emission tomography.¹⁵ Confirmation of disease is by tissue diagnosis with or without culture. FNA or biopsy reveals small spherical or oval yeast forms surrounded by a clear ring resembling a capsule, inside the cytoplasm of histiocytes. Treatment of the illness involves prolonged course of antifungals. Oral itraconazole is given in haemodynamically stable patients. Critically ill patients will require intravenous liposomal amphotericin B.¹⁶ There are no definite guidelines regarding monitoring the patients or regarding the duration of antifungal treatment in adrenal histoplasmosis.

Multiple mechanisms are implicated in the pathogenesis of adrenal failure in infective pathologies. Permanent damage of gland is due to granulomatous infiltration and adrenalitis as seen in our cases.¹⁷ Other mechanisms include the disturbance of the hypothalamic–pituitary–adrenal (HPA) axis due to physiological stress and release of cytokines and hypoadrenalism caused by drugs such as rifampicin and itraconazole that are used to treat infections.¹⁸

Diagnosing hypoadrenalism in any chronic illness can be very difficult due to overlapping clinical manifestations. Clinical differentiation of infectious cause of Addison's disease from an autoimmune aetiology may be challenging. Presence of fever and pulmonary symptoms along with imaging features like enlargement, calcification or atrophy of the adrenal gland are suggestive

of an infectious aetiology. The absence of other autoimmune features and autoimmune serological markers including antibodies against steroidogenic enzymes CYP11A1, CYP17 and CYP21A2 may also help in distinguishing between the two.¹⁹ However, these are non-specific features and most patients of Addison's disease warrant an imaging-guided biopsy of adrenal gland. Both glucocorticoids and mineralocorticoids should be replaced in a confirmed case of primary adrenal insufficiency. A combination of hydrocortisone (15–25 mg/day in two to three divided doses) and fludrocortisone (starting dose of 50–100 µg/day in adults) is the preferred regime. Titration of doses should be based on clinical assessment, electrolyte measurements and signs of toxicity.²⁰

In conclusion, an infectious cause should be suspected in any patient of Addison's disease presenting in a low/middle-income country. These causes are curable with antimicrobial chemotherapy; however, the reversal of function of the adrenal gland is uncertain. Larger studies are needed for formulating guidelines regarding duration of antimicrobial use as well as for optimal steroid therapy in the various infectious aetiologies of Addison's disease.

Learning points

- Infectious aetiologies remain the most common cause of adrenal failure in low/middle-income countries.
- Diagnosing adrenal insufficiency in the setting of a chronic infection can be challenging.
- Hypoadrenalism caused by infections can be permanent requiring lifelong replacement therapy even after treating the infection.

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