

Nonreversal of adrenal hypofunction after treatment of adrenal tuberculosis

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Tuberculosis of the adrenal glands is a common cause for Addison's disease in developing countries. Whether treatment of tuberculosis normalizes adrenocortical function in these patients is controversial. We are reporting two cases of Addison's disease because of adrenal tuberculosis, in whom treatment with antitubercular drugs did not restore normal adrenal functions. We conclude that treatment of tubercular Addison's disease does not lead to normalization of adrenocortical function.

Keywords:

Addison's disease, adrenocorticotrophic hormone stimulation, adrenal tuberculosis

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Introduction

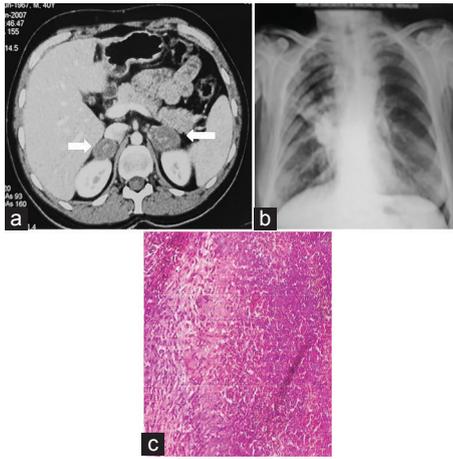
Tuberculosis continues to be a leading cause of primary adrenal insufficiency in developing countries, wherein around 50% of the patients of Addison's disease (AD) have tubercular etiology [1]. Because of rich vascular supply, adrenal glands are a common destination of involvement in patients with tuberculosis. Changes in size and function of the adrenal glands have been reported in patients with tuberculosis [2,3]. There have been conflicting reports regarding frequency and natural history of adrenal hypofunction in patients with tuberculosis before and after treatment [4–6]. We describe the clinical course of two patients of AD of tubercular etiology in whom adrenal function did not recover following completion of treatment of tuberculosis.

Case 1

A 31-year-old man was admitted in emergency with history of generalized malaise, weakness, fever, vomiting, darkening of skin, and postural giddiness of 1-week duration. Examination revealed an asthenic young person with dark complexion. He had tachycardia and low blood pressure with postural drop. His skin and buccal mucosa were pigmented; rest of systemic examination was normal. Investigations revealed a normal complete blood count with an erythrocyte sedimentation rate of 32 mm/first hour. Serum sodium was 130 mEq/l (normal: 136–145 mEq/l), serum potassium was 4.7 mEq/l (normal: 3.5–5.5 mEq/l), random plasma glucose was 123 mg/dl (normal: <200 mg/l), and serum calcium was 12.2 mg/dl (normal: 9–10.5 mg/l). Liver and kidney functions were within

normal limits. Radiographic chest and ECG were normal. A clinical diagnosis of AD with Addisonian crisis was made. A blood sample was taken for hormone estimations and patient was started on intravenous fluids and hydrocortisone. Subsequently, he was put on oral prednisolone (7.5 mg/day) and fludrocortisone (0.1 mg/day) with monitoring of clinical status, blood pressure, and electrolytes. Baseline serum cortisol collected in the emergency room at the time of initial admission was 7.75 µg/dl. Patient was investigated for the possible cause of AD; thyroid functions were within normal limits. Contrast-enhanced computed tomography abdomen revealed bilateral adrenal masses with calcification (Fig. 1). Computed tomographic (CT) chest and bone marrow aspiration did not show any evidence of tuberculosis in these areas. CT-guided fine needle biopsy of the adrenal mass revealed evidence of granulomatous lesion suggestive of tuberculosis (Fig. 1). Patient was put on antitubercular treatment (ATT) in the form of isoniazid, rifampicin, and pyrazinamide at appropriate doses. Patient while on ATT developed drug-induced hepatitis, which settled after cessation for some time. ATT was restarted and 1-year course of treatment was successfully completed. During therapy, patient was admitted with Addisonian crisis twice precipitated by respiratory tract infection and was appropriately treated. Patient was followed regularly after completion of ATT and was admitted for evaluation of adrenocortical reserve after 1 year. Prednisolone and fludrocortisone were stopped for a period of 5 days during which patient was kept under observation. Patient was subjected to prolonged adrenocorticotrophic hormone (ACTH) stimulation test with 250 µg of ACTH infusion for 24 h, and samples were drawn for estimation of cortisol at 0, 4,

Figure 1



(a) Computed tomographic abdomen showing bilateral adrenal enlargement with calcifications (arrow). (b) Chest radiographic posteroanterior view showing old fibrotic bands right mid and lower zones. (c) Histopathology of adrenal mass revealing granulomatous lesions suggestive of tuberculosis.

8, 12, 16, and 24 h. The cortisol levels at 0, 4, 8, 12, 16, and 24 were nonstimulable (Table 1).

Case-2

A 60-year-old woman, who had been treated for pulmonary tuberculosis 20 years ago, was admitted with clinical suspicion of adrenal insufficiency in view of easy fatigability, recurrent episodes of hypotension, and brownish discoloration of skin and mucous membrane. Investigations revealed normal complete blood count and kidney and liver function tests. Chest radiography showed a fibrotic band in the right midzone (Fig. 1). Workup for active tuberculosis, such as sputum for acid fast bacilli (AFB), Mantoux test, fiberoptic bronchoscopy and bronchoalveolar lavage for AFB, and urine for AFB, revealed no evidence of activity. Morning (8 a.m.) serum cortisol was 7.96 $\mu\text{g}/\text{dl}$ and post-ACTH peak cortisol was 11.23 $\mu\text{g}/\text{dl}$. CT abdomen showed bilateral adrenal masses and histopathology of the lesion was inconclusive. Patient was started on prednisolone (5 mg/day) and fludrocortisone (0.1 mg/day). Patient showed significant improvement in symptoms. After 6 months of treatment, patient was evaluated for reversibility of adrenocortical function. A 24 h ACTH stimulation test with 250 μg soluble ACTH infusion was performed to check for any stimulatibility of adrenal after stopping steroids for 4–5 days. Peak cortisol after ACTH test was 4.58 $\mu\text{g}/\text{dl}$ (Table 1).

Discussion

The clinical course of two patients, one with primary

Table 1 Cortisol response to prolonged ACTH stimulation^a

Time	0 h	4 h	8 h	12 h	16 h	24 h
	cortisol	cortisol	cortisol	cortisol	cortisol	cortisol
Case number 1	<1	1.43	3.3	2.07	1.66	1.24
Case number 2	3.42	4.16	4.58	3.92	3.0	2.9

ACTH, adrenocorticotrophic hormone; ^aStimulation by 250 μg of soluble ACTH, cortisol = $\mu\text{g}/\text{dl}$.

adrenal tuberculosis presenting with adrenal crisis and other with post-treated pulmonary tuberculosis and clinical adrenal insufficiency, is presented. Adrenal reserve in chronic infections especially tuberculosis has been a subject of controversy. Estimation of adrenal reserve assumes greater importance in view of the reports of sudden death and clinical deterioration in patients with commencement of antitubercular therapy [2–7]. In 1930, Guttman [8] reviewed 403 autopsy reports of patients with adrenal insufficiency. Adrenal tuberculosis was present in 70%, idiopathic atrophy in 20%, and other causes in 10%. In an autopsy series of 24 patients during 1928–1938, Dunlop [9] reported that 79% of cases had tuberculosis as cause of AD. However, subsequent studies have generally reported a declining proportion of tubercular AD. Nerup [10] reported that the majority (66%) had idiopathic type of AD, whereas only 7% had tuberculosis etiology. In developing countries, around 50% of the patients with AD have a tubercular etiology [1]. Prevalence of adrenal dysfunction in patients with tuberculosis has been studied with differing results. Ellis and Tayoub in a study on 41 African Zulus with acute pulmonary tuberculosis estimated the cortisol and androgen response to ACTH stimulation before and 2 weeks after starting treatment for tuberculosis. The proportion of nonresponders decreased from 50% before treatment to 30% after treatment; androgen function did not improve in any of the cases. Patients who received rifampicin as part of their treatment showed less improvement in adrenal corticosteroid function when compared with a group who did not receive rifampicin [11]. Barnes *et al.* [12] reassessed adrenal function in 90 adults with tuberculosis. Before treatment, 8% of the patients had a subnormal response to ACTH, which decreased to 1%, 4 weeks after starting ATT with a regime containing rifampicin. In a recent study, none of the 20 patients with active tuberculosis had any abnormality in ACTH-stimulated cortisol and aldosterone before and 5 days after rifampicin or ciprofloxacin-based ATT [13]. The variation in the results in these studies probably is in part due to different patient groups studied, the difference in methodology, and different standards used in interpretation of adrenal stimulation tests. Overt adrenal insufficiency is only seen after 90% of the cortex is destroyed, and recovery of an overt adrenal failure theoretically is not an expected outcome.

Bhatia *et al.* [6] studied the adrenocortical reserve by measuring the cortisol and aldosterone response to ACTH stimulation in five patients of AD before, 1 month, and 2–5 years after completion of ATT and concluded that adrenal function did not normalize in any of these patient. Both of our patients failed to show recovery of adrenal function after successful treatment of tuberculosis. In one of our recent study, we studied basal and stimulated cortisol levels at diagnosis and 6 months of treatment of pulmonary tuberculosis. Cortisol level was less in patients with pulmonary tuberculosis as compared with healthy controls and increases after ATT, although, unlike previous studies, none of the patients had adrenal insufficiency [14].

Conclusion

Two patients of AD of adrenal origin did not result in normalization of adrenocortical function after successful treatment of adrenal tuberculosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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