Isolated Adrenal Tuberculosis: Diagnostic and Therapeutic Difficulties

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Abstract

Primary adrenal insufficiency (PAI) is a rare disease and can masquerade many other conditions; hence resulting in diagnostic dilemma. Herein, we present the case of a 45 year old male patient who presented to the medical emergency with complaints of syncopal attack, generalised weakness, easy fatigability, salt craving and hyperpigmentation of skin and diagnosed as a case of adrenal crisis with urinary tract infection. Abdominal CT revealed bilateral adrenal enlargement with calcification with no evidence of extra-adrenal disease. Biochemically, low morning plasma cortisol, high plasma adrenocorticotropic hormone (ACTH) levels and short co-synacthen test were consistent with PAI. To look for etiology of PAI, endoscopic ultrasound guided fine needle aspiration (EUS-FNAC) was done which revealed positive Cartridge Based Nucleic Acid Amplification Test (CBNAAT) with rifampicin sensitive adrenal tuberculosis. The patient was started on antitubercular therapy, in addition to higher dose of glucocorticoid and mineralocorticoid replacement therapy. This case highlights that diagnosing bilateral adrenal tuberculosis without evidence of extra-adrenal tuberculosis, requires a high index of clinical suspicion and EUS-FNAC is an excellent non-invasive technique for histological adrenal sampling.

Keywords: TB; Adrenal Gland; Addisonian Crisis; ATT.

Introduction

In the developing countries, tuberculosis (TB) continues to be a significant cause of morbidity and mortality and one significant cause of primary adrenal insufficiency is adrenal gland tuberculosis. Conversely in developed countries 75-80% of cases of PAI are caused by autoimmune diseases (21-hydroxylase autoantibodies).[1] Approximately 12% of the patients with tubercular adrenalitis have no active extra-adrenal involvement.[2] Diagnosing these isolated adrenal TB is challenging and requires histopathological evaluation. EUS-FNAC is less invasive than both CT guided FNAC and laproscopic biopsy, but necessitates the expertise. This case report details a patient who presented with bilateral adrenal masses and adrenal crisis, without any indication of extra-adrenal TB.

Case Report

A 45-year old male presented with complaints of generalised weakness, easy fatigability and syncopal attack without any sensorimotor deficit and associated with significant weight loss of ~6 kg in the last 6 months. At the time of presentation, the patient reported 2 episodes of syncopal attacks associated with palpitation for which he sought medical care. There was history of reduced urine output and burning micturition. The patient was not a known case of any chronic medical or surgical illness. On the basis of above history patient was initially treated as a case of urinary tract infection with sepsis. Patient further revealed that he noticed the darkening of skin and mucous membrane for past 6 months [Figure 1 (A), (B), (C)]. The patient added that he first noticed the blackish discolouration of face, lips

and neck, gradually progressed over skin involving his entire body, over a period of 6 months. The patient frequently experienced salt cravings and used to add 1-2 table spoon of salt in each meal. On examination, the patient had emotionally labile mood and affect. The patient had orthostatic hypotension and generalized hyperpigmentation of skin, nails, axillae and buccal mucosa with sparing of dorsum of tongue.

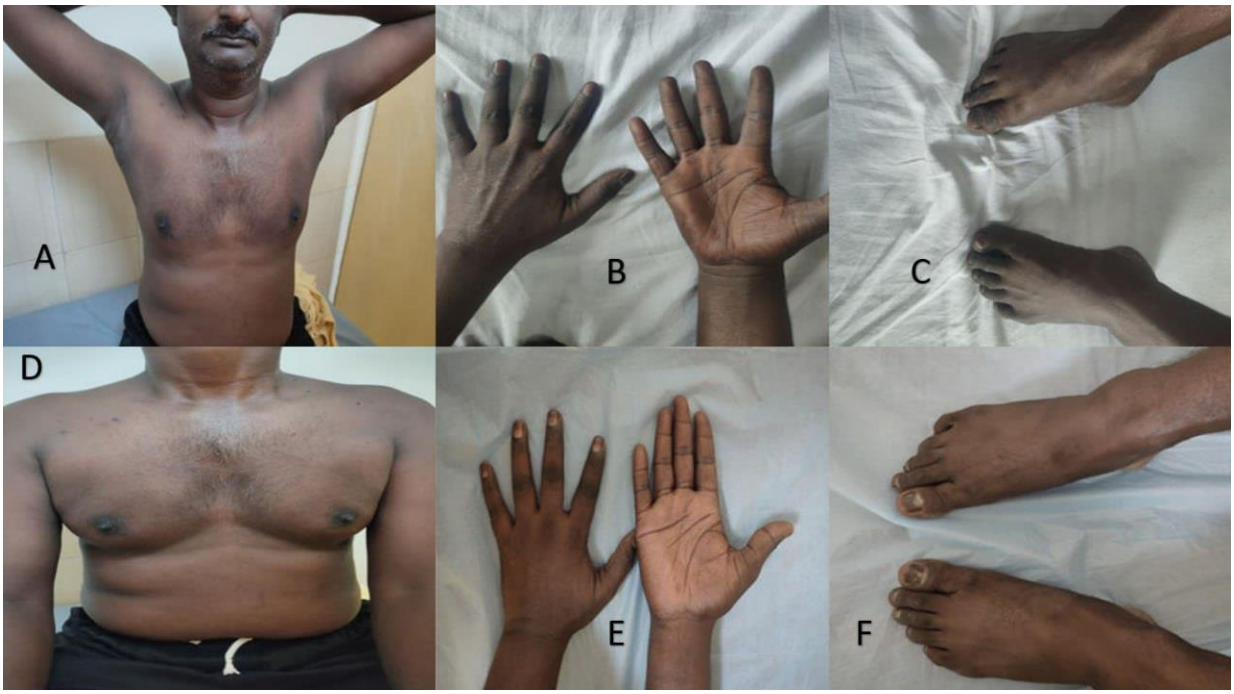

Figure 1: Hyperpigmentation of the skin at diagnosis (A,B,C) and four months post therapy (D,E,F).

Initial investigation revealed hemoglobin of 15.1 gm/dl, hematocrit of 55%, and mild leucocytosis with eosinophilia (Absolute Eosinophil Count-750/mm^3). Blood sugar was 79 mg/dl, serum urea was 55mg/dl and creatinine 1.9mg/dl. Arterial Blood Gas (ABG) analysis revealed normal anion gap metabolic acidosis with serum potassium level of 7.2 mEq/L and sodium level 123.0 mEq/L. Thyroid profile showed normal T3/T4 levels with Thyroid Stimulating Hormone (TSH) of 8.98 (0.46-4.6 mcg/ml). Liver function test (LFT)/Cardiac enzymes(CPK and trop I) were within normal limits and urine culture was sterile. In view of generalized hyperpigmentation with dyselectrolytemia, random serum cortisol level was sent which was low, 75.14 nmol/L (ref 134-636 nmol/l). To confirm the diagnosis, serum Adreno Cortico Trophic Hormone (ACTH) level was estimated which showed elevation of serum ACTH value of 1586pg/ml (ref. 10-60 pg/ml). Short Synacthen Test (SST) was done with 250 microgram of cosyntropin, which showed no rise in serum Cortisol values after 30 minutes and 1 hour of giving cosyntropin and confirmed the diagnosis of primary adrenal insufficiency [Table 1].

Table 1: Short Synacthen Test (SST) with serum cortisol at 0, 30 minute and 1 hour.

Timing		**Cortisol level (nmol/L)**
8:00 am	0 hour	74.26
8:30 am	30mins	37.99
9:00 am	1 hour	37.22

Additional investigations were done to look for etiology of PAI [Table 2]. Contrast Enhanced Computed Tomography (CECT) chest and abdomen revealed bilateral bulky adrenal glands with multiple foci of coarse calcification in bilateral adrenal parenchyma [Figure 2]. To look for an occult malignancy, a Positron Emission Tomography (PET) CT was also done which showed no evidence of metabolically active disease noted anywhere. An EUS-FNAC from the bulky adrenal glands was performed the aspirate was examined for Gram stain, Periodic acid schiff stain (for fungal spores and hyphae) and fungal culture but all the investigations were negative. The aspirate

was then tested for CBNAAT for TB bacilli which showed the presence of Mycobacterium Tuberculosis (Rifampicin Sensitive) and culture grew mycobacterium tuberculosis, sensitive to the primary antitubercular therapy.

Table 2: Various investigation done for PAI with bilateral adrenal mass.

Parameter	Value	Parameters	Values
Sputum AFB/CBNAAT	Negative	Serologies EBV/CMV/HSV	Non reactive
HIV I/II	Non reactive	Tumour markers	18.6 (15-36) (ng/ml)
HBsAg	Non reactive	• CA 19-9	2.10(1.2-4) (mmol/L)
Anti HCV	Non reactive	• CEA	20(15-36.7) (nmol/L)
		• PSA	1.7(0.8-2.6)(mmol/L)
		• AFP	
ESR	31 mm/hr	ANA	Negative
Montoux	Non reactive	Anti ds-DNA	Negative
Urine for AFB	Negative	C-ANCA/p-ANCA	Negative
CRP	8 mg/dl	LH	5.6 (1.8-6.0) (ng/ml)
		FSH	1.05 (0.5-0.9) (ng/ml)
		Estrogen	3.5(12.8-28.4) (ng/ml)
		Progesterone	1.02(2.5-61.8) (ng/ml)
		Testosterone	17.8(12.2-24) (ng/ml)
CD4 count	1534/mm^3	Serum ferritin	418 (261-441) (mg/dl)
ACE	20 nmol/ml/min	Hba1c	5.6%

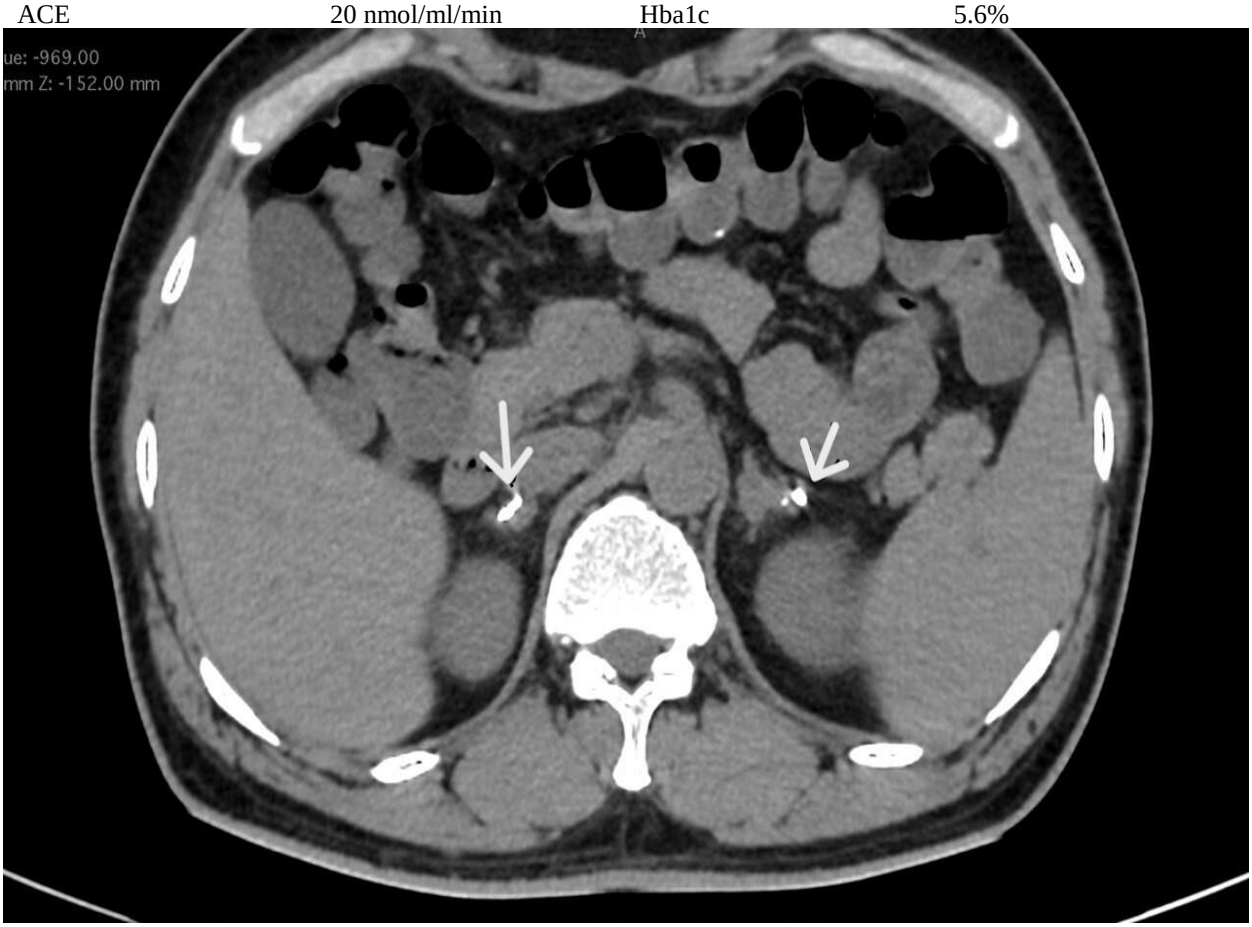

Figure 2: CECT abdomen showing bulky adrenals with multiple foci of coarse calcifications.

The patient was initially resuscitated with intravenous fluids and I.V. antibiotics. Injection hydrocortisone was started 300mg IV route in 3 divided doses on day 1 and tapered subsequently (Day 1: 300mg, Day 2: 200mg, Day 3: 100 mg). Once the diagnosis of primary adrenal insufficiency due to adrenal TB was established, ATT was started along with oral hydrocortisone 30mg cumulative once daily dose [20mg (8:30 am) + 5mg(1:30 pm) + 5mg (4:30 pm)] keeping in accordance to normal circadian rhythm along with Fludrocortisone 100 micrograms.

Discussion

The clinical presentation of PAI depends on its rate of onset and severity. Diagnosing PAI can be challenging due to the non-specificity of presenting symptoms. The most common manifestations are weakness, fatigue, weight loss, anorexia, nausea, vomiting, hypotension, and skin hyperpigmentation. Hyperpigmentation of skin, salt craving and orthostatic hypotension are more specific of PAI is due to reduced mineralocorticoid function.[3] Primary adrenal insufficiency (PAI) can be caused by autoimmune causes like adrenalitis, autoimmune polyglandular syndrome, infections like tuberculosis, histoplasmosis, CMV and metastasis to the adrenals.[3] Isolated adrenal tuberculosis is rare, and accounts for 1-2% of the etiologies of adrenal masses called incidentalomas.[4] Bilateral adrenal glands are frequently (>80%) affected by the hematogenous or lymphogenous dissemination of TB.[5] Before adrenal insufficiency develops, the adrenal gland must be damaged to at least 90% of its original size by caseous necrosis.[6] Therefore, it is unlikely that adrenal function would improve following medication, necessitating lifelong replacement therapy. In PAI there is mineralocorticoid deficiency with normal or low plasma aldosterone level and raised plasma renin concentration resulting in depletional hyponatremia (90%) and hyperkalemia (65%). There can be moderately elevated TSH values due to direct effect of glucocorticoid deficiency and reverses with replacement therapy. Morning (8AM) plasma cortisol concentrations of <83 nmol/L (or 3 μg/dL) and elevated plasma ACTH (>100pg/ml) levels are almost confirmatory of primary adrenal insufficiency. When test is equivocal, the diagnosis is confirmed by cosyntropin stimulation test (CST).[7] The diagnosis of PAI in our index case was established post CST.

CT or MRI findings of adrenal tuberculosis (TB) is characterised by bilateral adrenal enlargement, peripheral rim enhancement, low density in the core region, and preservation of contour in the early stages, followed by reduced size and calcification in the later stages.[5] PAI with bilateral enlarged adrenal mass on the CT scan and active extra-adrenal tuberculous diseases, especially in areas with a high burden of tuberculosis may not require adrenal biopsy. However, our patient had no evidence of extra-adrenal tuberculosis; therefore, an adrenal biopsy was indicated to establish the diagnosis. We opted for EUS guided fine needle aspiration of the adrenal mass as it is safer than CT guided biopsy or laparoscopic adrenalectomy. Previous cases of isolated adrenal tuberculosis is either diagnosed by laparotomy, laproscopy or CT-guided biopsy.[1,8] Our case is likely the first case of isolated adrenal TB diagnosed by EUS-FNAC. Diagnosis of adrenal TB includes histopathology evidence of necrosis caseosa area, Datia-Langhans cell and tissue sample positive for Zn stain, PCR and a culture growth. Concurrent treatment of PAI and TB can be challenging as rifampicin is a strong inducer of the cytochrome P450 CYP3A4 system leading to increased cortisol metabolism, and thus may also cause an adrenal crisis indicating that the dose of supplemental steroid should be adjusted when the enzyme inducer is started or stopped.[9] Therefore we increased the dose of hydrocortisone to 30 mg cumulative once daily dose after rifampacin was added as ATT in our patient.The patient is currently on regular follow up with improved appetite, weight gain, and normalisation of skin pigmentation without any relapse of the disease [Figure 2 (D), (E), (F)].

This case report illustrate the a step-by-step approach for establishing a diagnosis of bilateral adrenal masses with isolated adrenal TB. Where a combination of clinical judgement, biochemical, hormonal, radiological and histopathological evaluation is required. It also highlights importance of EUS-FNA as a less invasive method to diagnosed bilateral adrenal masses.

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