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A Case Series Of Primary Adrenal Insufficiency Of Infectious Etiology (Tuberculous Adrenalitis) Presenting As Gastrointestinal, Systemic And Cutaneous Manifestations -A Single Center Experience From Andhra Pradesh

B.S.V.V. Ratnagiri [1], Lella Padmaja [2], Sai Bhavishya Dasari [3], Pusuluri Naga Vamsi[4], Chittajallu Leela Venka Krishna [5], M.Jagan Mohan [6], Srivani Reddy Anireddy [7], Chitte Hema Nikhil [8]

Associate Professor, Department Of Gastroenterology, Siddhartha Medical College, Vijayawada, A.P, India
Tutor, Department Of Obstetrics And Gynecology, Siddhartha Medical College, Vijayawada, A.P, India
Intern, Siddhartha Medical College, Vijayawada, A.P, India
Post Graduate, Department Of General Medicine, Siddhartha Medical College, Vijayawada, A.P, India
Post Graduate, Department Of General Medicine, Siddhartha Medical College, Vijayawada, A.P, India
Professor & HOD, Department Of Gastroenterology, Siddhartha Medical College, Vijayawada, A.P, India
Post Graduate, Department Of General Medicine, Siddhartha Medical College, Vijayawada, A.P, India
Intern, Siddhartha Medical College, Vijayawada, A.P, India
Intern, Siddhartha Medical College, Vijayawada, A.P, India

Abstract:
Addison's disease presents with chronic and progressive fatigue, muscle weakness, lightheadedness with gastrointestinal symptoms (nausea, diarrhea, vomiting, and weight loss) and hypotension and hyperpigmentation with lab abnormalities such as hyponatremia and hyperkalemia with normal anion gap metabolic acidosis with low cortisol and raised ACTH, that even after receiving cosyntropin stays low. The most common etiologies are autoimmune adrenalitis in developed countries and TB in developing countries. We present a case series of 2 different case reports with various manifestations of primary adrenal insufficiency of infectious etiology(extrapulmonary tuberculosis). The importance lies in the fact that extrapulmonary TB can present with a wide range of symptoms mimicking other diseases. Primary adrenal insufficiency is rare but one such presentation often leading to late diagnosis increasing morbidity and mortality. This case series highlights the importance of considering TB as one of the differential diagnoses for unexplained adrenal insufficiency even in the absence of a history of tuberculosis.

Keywords: *Addison's disease, extra pulmonary Tuberculosis, tuberculous adrenalitis*

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I. Introduction:

When Thomas Addison described his patients with adrenal cortex insufficiency in 1855, all cases were due to the destruction of the adrenal cortex by *Mycobacterium tuberculosis.* Tuberculosis is an airborne infectious disease commonly caused by Mycobacterium tuberculosis which primarily affects lung parenchyma but presenting with symptoms of adrenal insufficiency is an uncommon presentation. Primary adrenal insufficiency also called Addison's disease (AD)[1],[2],[3]is a rare endocrine disorder characterized by adrenal cortex hypofunction due to intrinsic adrenal pathology.75–80% caused by autoimmune destruction of the adrenal gland and TB account for 7–20% of Addison's Disease[4]. Other causes include invasion of glands by neoplastic cells, CMV virus, histoplasmosis, HIV, hemochromatosis, amyloidosis, hemorrhage, and surgical removal of glands. The clinical picture is due to deficiency of glucocorticoids and mineralocorticoids resulting from the failure of the adrenal cortex. Addison's disease gradually presents with chronic fatigue, weakness, nausea, vomiting, loose stools , weight loss , dizziness, and pigmentation disorders .Due to rarity of disease and nonspecific symptom manifestations lead to delay in diagnosis and acute presentation in adrenal crisis which increases morbidity and mortality.we present a case series of AD caused by tuberculous adrenalitis presented as the only manifestation of extrapulmonary tuberculosis, discovered in the diagnostic workup of gastrointestinal symptoms.

CASE 1

A 52-year-old male with progressive fatigue with recurrent nausea and vomiting, lightheadedness, dizziness, and anorexia since 3 months was admitted for the same.The patient had no history of fever, cough, rash, or back pain.patient is not a known case of diabetes, hypertension or thyroid disorder and he has no other medical conditions he does not use drugs,tobacco, or alcohol, with not significant family history.

Clinical examination:
patient is drowsy with signs of moderate dehydration
blood pressure is 90/60mmHg supine and 70/50mmHg standing
PR: 112 bpm
SpO2; 98%on RA
Temperature:a febrile
Skin showed signs of moderate dehydration and generalised hyperpigmentation of sun exposed areas

Investigations:
Complete blood picture was within normal limits with Haemoglobin :13.7g/dL
Total WBC count 7.96 thousand/cumm
Serum electrolytes: sodium [Na+] :120 mmol /L; potassium [K+]:4.0mmol/L; Chloride [Cl-]:97 mmol/L
Serum Cortisol (morning):0.60 mcg/dl (6.7-22.6)[5'
Serum Cortisol (evening):0.41 mcg/dl
Plasma ACTH:1837.00pg/ml (4.7-48.8)
Serum Aldosterone :0.97ng/dl
Renin direct -plasma 13.90ng/ml/hr
Total T3 :95.6ng/dl (87-178 ng/dl), Total T4 13.9mcg/dl (4.82-15.65mcg/dl), Thyroid Stimulating hormone(TSH): 1.30
C-Reactive protein :114mg/L
Blood glucose :83mg/dl
Serum creatine:1.2mg/dl
Blood urea :22mg/dl

Mantoux test:Negative
Interferon-gamma release assay (IGRA TB Gold)-whole blood :positive
HIV 1 and 2 :Negative
HBSAg :Negative
HCV:Negative
VDRL :Negative

MRI BRAIN PLAIN sella,pituitary and parasellar regions are normal and no significant abnormality was detected in brain parenchyma.
CECT ABDOMEN Abdomen and pelvis:Both adrenal glands are dysmorphic with loss of normal morphology. Left adrenal gland is atrophic .Right adrenal gland is mildly bulky showing central smooth calcifications.[6]
ADRENAL BIOPSY could not be acquired.
THERE WAS NO EVIDENCE OF TB INFECTION ELSEWHERE.

Treatment: patient was started on corticosteroid replacement therapy and anti-tubercular therapy according to INDEX TB guidelines.[7],[8]

Fig1 And 2: Generalised Hyperpigmentation On Sun-Exposed Areas Of Case 1

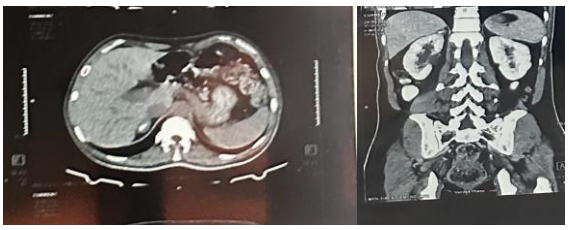

Fig3 And 4: CT Scan Of The Abdomen Of Case 1

Case 2

Case presentation:

A 40-year-old male patient was admitted with a history of nausea, vomiting, loss of appetite, loss of weight and severe fatigue since 4 months. He denied any history of fever, cough, rash, back pain, drug intake, or any history of convulsions. His past history was positive for tuberculosis and had taken ATT for 6 months. He was not a known hypertensive but diabetic having treatment since 1 year.He was treated with nonspecific supportive therapies in primary care hospital, before getting admitted in our ward.

Clinical examination:

The patient is sick-looking and is conscious, and coherent with signs of mild dehydration. He had hyperpigmentation of hands (creases), elbows and feet. PR: 78/min, BP: 90/60 mm hg, Respiratory rate: 18/min. Afebrile. Respiratory system: Bilateral air entry present with normal vesicular breath sounds. Per abdomen: Soft and no organomegaly. Cardiovascular system: Normal

Investigations:

Case report Complete blood count (CBC) showed normal. Hb 13.2 g/dl, white blood cells 7,000/cram with normal platelet count. ESR 40mm/1g hour.

Serum Creatinine is 2.2mg/d1. The sodium was: 128 mmol/L, potassium was 6.5 mmol/L, chlorides were 89mmol/L.

Normal liver function tests. Chest X-ray – Normal. Ultrasound of the abdomen showed bilaterally enlarged adrenals with calcification, small hemorrhages and thickened ileocaecal junction noted (possibly of Koch's etiology).

CT scanning of the abdomen showed bilaterally enlarged adrenals with small hemorrhages and speckled calcifications. Mantoux test was negative. PCR for Tuberculosis is positive.

Early morning serum cortisol was very low (0.25ug/c11). The adrenocorticotropic hormone (ACTH) level was very high (1250pg/ml). The gonadotrophic hormones, prolactin and thyroid function tests were within normal limits.

The serology for HIV 1 and 2 were negative.

Diagnosis: History, clinical examination, and laboratory work up confirmed the diagnosis of Addison's disease secondary to tuberculosis.

Treatment: The patient was kept on hormonal supplementation (cortisol) and anti-tuberculous treatment (ATT.)

Fig 5 And 6 Hyperpigmentation In Case 2

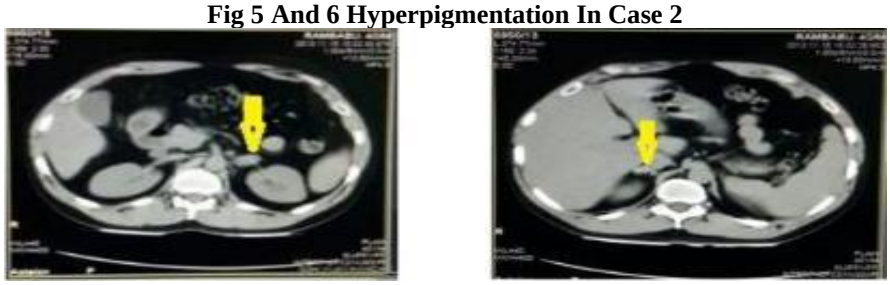

Fig 7 And 8: Enlarged Left Adrenal With Hemorrhage In Case 2

II. Discussion:

Addison's disease is a primary adrenocortical deficiency that is the result of damage to the cortex. Overt clinical features of hypoadrenalism occur when 80-90% of both adrenal cortices are destroyed.Addison's disease usually manifests as an insidious and gradual onset of nonspecific symptoms, often resulting in a delayed diagnosis.Primary adrenal insufficiency generally manifests as weakness,anorexia,gastrointestinal symptoms,postural dizziness and or pigmentation disorder.The two major causes of Addison's disease are autoimmunity[9] and tuberculosis.Tuberculosis may affect many of the endocrine glands including the hypothalamus, pituitary, thyroid, but the most commonly involved endocrine organ is the adrenal gland. In addition to mycobacterial tuberculosis, other mycobacterium, bacteria, viruses and fungi may affect the adrenal glands and lead to the development of adrenal insufficiency. Most cases of adrenal tuberculosis are found 10 to 15 years after the initial infection. Hence, tuberculous [10]Addison's disease has a relatively late onset.In the above presented case extrapulmonary tuberculosis manifested as adrenal insufficiency with no prior history of tuberculosis and in the other adrenal involvement was present even after completion of treatment.Both cases have hyperpigmentation due to increased levels of ACTH which stimulate melanocytes.

Enlargement of both adrenal glands may occur in most (90%) patients with Tuberculous adrenal insufficiency[11].CT is the preferred imaging examination for adrenal tuberculosis and has suggestive significance for diagnosis, disease activity and prognosis.The imaging findings may vary with the stage and activity of the inflammatory process. In early Tuberculous Adrenalitis, bilateral adrenal enlargement is the typical finding, as in the present case. At the late or healing stage, enlargement of Tuberculous adrenals may partially or completely resolve, with or without calcification or atrophy.

It has been stated that, adrenal enlargement may be due to activation of the hypothalamus-pituitary-adrenal axis during active pulmonary tuberculosis, as active pulmonary tuberculosis is a stressful condition with direct involvement of adrenal glands by infection. In the present cases, the patients were started on anti-tuberculous treatment along with replacement therapy.Recovery of adrenal function may occur in patients treated for Tuberculosis, but the absence of adrenal recovery 2 to 5 years after therapy also has been observed.

III. Conclusion:

The cases presented showed variable manifestations of TB adrenalitis.The first case has no prior history of Tuberculosis. The second case has previously completed ATT for 6 months, by the end of the course the CBNAAT and sputum smear came negative but has ongoing slow infection left over in the adrenals leading to addisons eventually.

The cases presented with gastrointestinal symptoms and hyperpigmentation of skin with involvement of adrenal glands presenting in primary adrenal insufficiency. The importance of these cases lies in the fact that tuberculosis should be ruled out as the cause of Addison's disease in disease-prevalent areas even with no prior history as corticosteroid replacement therapy may flare up any residual tuberculous foci. Timely initiation of anti-tubercular treatment, coupled with corticosteroid replacement in cases of adrenal failure, is critical for favorable outcomes. Further research is needed to establish standardized protocols for diagnosis and management, as well as to explore long-term outcomes in affected individuals. Increased awareness among clinicians is essential to improve early detection and treatment efficacy.

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