Special Feature: Undergraduate corner

Addison's disease

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Addison's disease is a rare endocrine condition.[1] It can be seen either as a part of autoimmune polyglandular syndrome or as an isolated entity.[2] This condition is easily overlooked due to commonly encountered non-specific presenting symptoms. Early identification of this condition and treating the same is of paramount importance as any illness like infections can precipitate the adrenergic crisis in these patients.

Case History

A 37-year-old lady presented with gradual onset of generalized darkening of skin and generalized weakness of six month duration. She had occasional giddiness and vomiting for 4 months. Hyperpigmentation was progressive and was more on the palms and outer aspect of hands and the oral cavity; hypopigmented patch was noticed over the lower lips and both palms. Patient experienced generalized weakness which was gradual in onset. She was lethargic in carrying out activities of daily living. She had recurrent episodes of giddiness which was associated with nausea and vomiting and felt relieved on lying down and taking rest. She had intermittent 'low grade' fever lasting for 2 to 3 days during 3 months prior to her presentation. She had occasional epigastric discomfort and decreased appetite during 2 months prior to presentation. She also noticed thinning of hair on the scalp. There was no history of white patches in the oral cavity, abdominal pain, and difficulty in swallowing food, steatorrhoea, weight loss, constipation, diarrhoea, yellowish discoloration of the eyes or passage of high coloured urine. There was no salt craving, loss of consciousness, headache, neck pain, tinnitus, loss of hearing, double vision, weakness of the limbs or drooping of eyelids. Further, there was no history of cough, breathlessness, expectoration, dysuria, swelling of feet, swelling in the neck, cold intolerance, loss of hearing, palpitations, tremors or sweating in the hands, polyuria and polydipsia. No history of parasthesias in the limbs or perioral parasthesias, carpal spasms or stridor was recorded. There was no history of blisters on the skin, photosensitivity, pitting of nails. There is no prior documentation of diabetes mellitus, systemic hypertension, coronary artery disease, or cerebrovascular disease, tuberculosis or thyroid disorder in the past.

She attained menarche at the age of 13 years and had regular menses till 4 months prior to the presentation. Since then she was amenorrhoeic. There was history of multiple consultations for the episodes of giddiness during which she was always found to be in hypotension and was usually managed with intravenous fluids every time. She received antipyretics for the fever which subsided subsequently.

Physical examination revealed moderate built and nourishment; height 1.49 m, weight 54 kg, BMI 24.3 kg/m^2; and body surface area (BSA) 1.54 kg/m^2. Pallor was present; there was no icterus, cyanosis, clubbing, lymphadenopathy, pedal oedema or goitre. Generalized hyperpigmentation of the skin with darkening of the palmar creases, vitiligo patches over the lower lip and both the palms, thinning of the hair on the scalp and normal nails, were noted. Her pulse was 84 beats/min, regular, normal volume; blood pressure was 130/86 mm of Hg in supine position and 112/80 mm of Hg in sitting posture. Fundoscopy was normal. All

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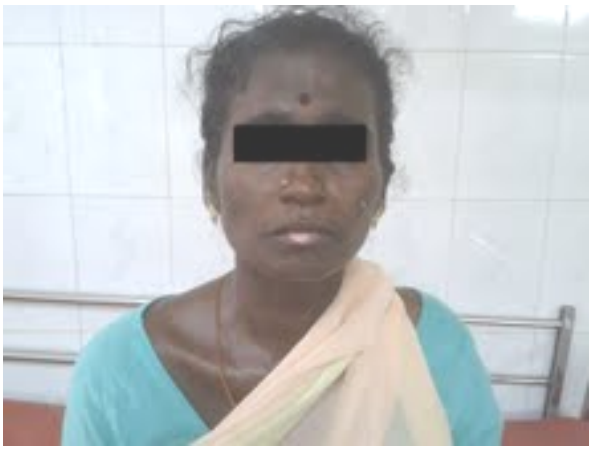

Figure 1: Clinical photograph showing the patient with darkening of skin and vitiligo patch on lower lip

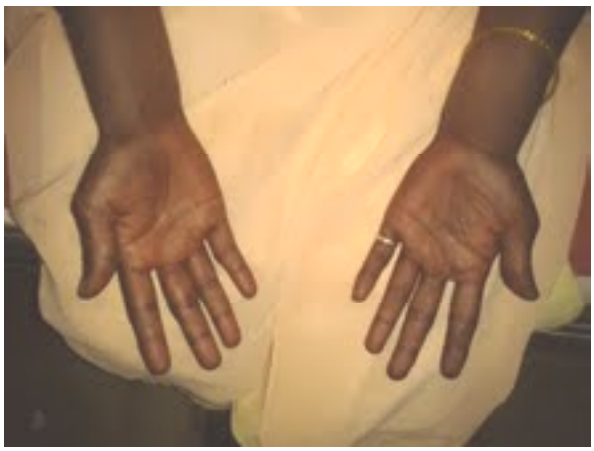

Figure 2: Clinical photograph showing darkening of palmar creases and vitiligo patches

other systems were essentially normal. A clinical diagnosis of Addison's disease was suspected and the patient was worked-up for the same.

Her laboratory results were as follows: liver function tests were normal, serum, total proteins 6g/L, serum albumin 3.4g/L, fasting blood glucose 90 mg/dL, postprandial blood glucose :120 mg/dL, haemoglobin 10 g/L, packed cell volume 30%, white blood count 5,800/mm^3, neutrophils 33%, lymphocytes 61%, eosinophils 6%, platelets adequate and normal erythrocyte sedimentation rate 12 mm at the end of the first hour. Peripheral smear showed microcytic hypochromic picture. Cosyntrophin test was performed using 250 μg of synthetic adreno corhicotrophin hormone (ACTH) and blood was collected after 30 and 60 minutes for the estimation of serum cortisol. Her base-line cortisol level is 4.3 μg/dL. Serum cortisol levels following cosyntropin administration were 4.6 μg/dL and 4.0 μg/dL (normal >18 μg /dL) at 30 and 60 minutes respectively. Serum sodium was 125 meq/L, chloride 100 meq/L, postassium 5.6 meq/L, blood urea 28 mg/dL, serum creatinine 0.9 mg/dL. Her thyroid function tests were normal. Serological testing for human immune deficiency virus (HIV) -1 and -2 was negative. Serum follicle stimulating hormone (FSH), plasma renin and aldosterone activity could not be estimated.

Radiological investigations including abdominal ultrasonography, chest radiograph, plain radiograph of the abdomen, computed tomography (CT) of the abdomen were normal. With all these findings the patient was diagnosed to have Addison's disease due to autoimmune aetiology.

She was prescribed cortico steroid replacement with oral prednisolone 5 mg once daily, fludrocortisone - 0.1 mg once daily and iron supplementation. Counselling on stress management was arranged for the patient and her relatives before patient was discharged.

At one month follow up her weight increased by 0.5 kg, blood pressure was 130/80 min Hg in supine postion and 120/80 mm Hg in standing position. She was actively partaking in her daily activities, household chores. Vomiting ceased. Her attendants also found her active. Hyperpigmentation decreased to some extent.

What is Addison's disease?

Thomas Addison (1855)[4] first described the clinical features of primary adrenal insufficiency, hence the disease has been eponymously called Addison's disease. The characteristic form resulting from primary adreno-cortical insufficiency distinguishes Addison's disease from other forms of adrenal insufficiency which may result from pituitary or hypothalamic diseases with decrease in ACTH secretion and consequent adrenal cortex atrophy. In Addison's disease there is destruction of the adrenal cortex resulting in inadequate secretion of the adrenal cortical hormones, namely, cortisol,

aldosterone and androgens. Cortisol, the main hormone affected in the disorder is important in the body's ability to cope with stressful situation such as infection, hypotension, and surgical procedures. The hypothalamic-pituitary-adrenal axis is involved in regulation of adrenocortical function. Addison's disease is a term restricted to primary adrinocortical insufficiency. Other secondary or tertiary causes of adrcnocortical insufficiency are not included under the term, 'Addison's disease'. Primary adrenal insufficiency can be a life threatening disorder particularly in stressful situation, as cortisol secretion cannot be increased on demand at all.[3]

What are the causes of Addison's disease?

Primary adrenal insufficiency is most commonly caused by autoimmune adrenalitis. Adrenal insufficiency as part of autoimmune polyglandular syndromes (APS) accounts for 60%-70%, isolated autoimmune adrenalitis accounts for 30%-40%. Others causes are tuberculosis, fungal infection, metastatic neoplasia, hemochromatosis and congenital adrenal hyperplasia, adrenoleukodystrophy.[7]

What are the differences between various types of autoimmune polyglandular syndromes?

APS1, also termed autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is the cause in 10% of patients affected by APS. It is transmitted in an autosomal recessive manner and is caused by mutations in the autoimmune regulator gene AIRE. Associated autoimmune conditions overlap with those seen in APS2, but may also include total alopecia, primary hypoparathyroidism and in rare cases lymphoma. APS1 patients invariably develop chronic mucocutaneous candidiasis usually manifest in childhood and preceding adrenal insufficiency by years or decades. APS2 is the much more prevalent and is of polygenic inheritance, with confirmed associations with the human leukocyte antigen (HLA)-DR3 gene region in the major histocompatibility complex and distinct gene regions involved in immune regulation like cytotoxic T-lymphocyte antigen 4 (CTLA 4), protein tyrosine kinase, non-receptor type 22 (lymphoid) (PTPN 22) and C-type lectin domain family 16 (CLEC 16A). The most frequently associated autoimmune disease includes thyroid autoimmune disease, vitiligo, and premature ovarian failure. Less commonly, additional features may include type 1 diabetes mellitus and pernicious anaemia caused by vitamin B_{12} deficiency.[7]

Which is the most specific sign of Addison's disease?

Addison's disease may manifest with diverse and nonspecific clinical and/or biochemical features.[3,5] The most specific sign of primary adrenal insufficiency is hyperpigmentation of skin and mucosal surfaces associated with fatigue and weight loss.[3]

What are the features of Addison's disease?

In a study[5] of 50 patients seen over a period of 17 years the following features were described in patients with Addison's disease: hyperpigmentation (86%), weight loss (67%), abdominal pain (20%) and diarrhoea (16%). However, the disease may present atypically and requires a high index of suspicion for diagnosis.[3,6]

How do you manage a patient with Addison's disease?

Glucocorticoid replacement for the treatment of chronic adrenal insufficiency should be administered at a dose that replaces the physiologic daily cortisol production, which is usually achieved by the oral administration of 15-25 mg hydrocortisone in two to three divided doses. In all patients, at least one-half of the daily dose should be administered in the morning. Monitoring of glucocorticoid replacement is mainly based on the history and examination for signs and symptoms suggestive of glucocorticoid over or under replacement, including assessment of body weight and blood pressure. Mineralocorticoid replacement in

primary adrenal insufficiency should be initiated at a dose of 100-150 μg fludrocortisone. The adequacy of treatment can be evaluated by measuring blood pressure, sitting and standing, to detect a postural drop indicative of hypovolemia. Adrenal androgen replacement is an option in patients with lack of energy, despite optimized glucocorticoid and mineralocorticoid replacement. Patients living or travelling in regions with delayed access to acute health care should carry a hydrocortisone self-injection emergency kit, in addition to their usual steroid emergency cards and bracelets.[7]

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