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Case Report

Diabetes mellitus masking an ectopic Cushing syndrome in a young male: a case report

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ABSTRACT

Ectopic adrenocorticotropic hormone (ACTH) secretion is a rare but important cause of Cushing syndrome, often associated with neuroendocrine tumors such as bronchial or gastrointestinal carcinoids. Its presentation can be subtle or atypical, delaying diagnosis and increasing morbidity. Herein this case report presents a 24-year-old male presenting with uncontrolled diabetes mellitus, polyuria, and weight loss (13 kg over 6 months). He exhibited proximal muscle weakness, broad purple striae, and extensive hyperpigmentation. Laboratory evaluation revealed markedly elevated 8 am serum cortisol 82 mcg/dl, midnight awake cortisol 211 mcg/dl, overnight dexamethasone suppression test (27.32 mcg/dl), plasma ACTH 320 pg/ml, and a non-suppressed (<50%) high-dose dexamethasone suppression test (16 mcg/dl). High-resolution computed tomography (HRCT) chest demonstrated multiple pulmonary nodules. Ga-68 DOTANOC PET-CT imaging revealed somatostatin receptor expression in bilateral lung nodules. Endobronchial biopsy confirmed atypical carcinoid tumor, Ki-67 index 4%. This case highlights the diagnostic complexity of ectopic ACTH syndrome, particularly in young adults presenting with rapidly worsening diabetes. The presence of significant pigmentation, proximal myopathy, and metabolic derangements were key clinical clues. Atypical carcinoid tumors exhibit intermediate biological behavior and require a multidisciplinary management approach including surgical resection, somatostatin analog therapy, and cortisol-lowering strategies. Ectopic ACTH syndrome should be considered in young patients with severe metabolic abnormalities, rapid weight loss, and hyperpigmentation. Early recognition and appropriate work-up can prevent complications and improve outcomes.

Keywords: Ectopic Cushing syndrome, ACTH-dependent cushing, Atypical carcinoid tumor, Neuroendocrine tumor, Hypercortisolism

INTRODUCTION

Cushing's syndrome arises due to prolonged exposure to abnormally high levels of circulating glucocorticoids.[1] The most prevalent cause of Cushingoid symptoms is iatrogenic corticosteroid usage, but several herbal medicines can also raise circulating corticosteroid levels, leading to Cushing syndrome.[2,3] In contrast, endogenous Cushing's syndrome is uncommon, with an estimated yearly incidence of about 2–3 cases per million people.[3] Although Cushing's disease presents with classic signs such as moon face, facial plethora, striae rubrae, and fat accumulation over supraclavicular and dorsal regions, its clinical picture often mimics common metabolic disorders. Cushing's disease is frequently associated with comorbidities like visceral obesity, hypertension, diabetes, and dyslipidemia features overlapping with metabolic syndrome, and may also involve reproductive dysfunction, neuropsychiatric disturbances, and skeletal complications.[4,5]

Endogenous Cushing's syndrome arises through two main mechanisms: adrenocorticotropic hormone (ACTH) - dependent forms (about 80% of cases), typically due to pituitary adenomas or ectopic ACTH-producing tumors, and ACTH-independent forms (about 20%), resulting

from autonomous adrenal cortisol secretion caused by benign or malignant nodules or bilateral micro- or macronodular adrenocortical hyperplasia.[6] Early diagnosis of Cushing's syndrome is crucial but often challenging due to its overlap with common conditions like pseudo-Cushing's syndrome. Evaluation should begin by excluding exogenous corticosteroid use. First-line screening includes the 1-mg dexamethasone suppression test, 24-hour urinary free cortisol, and late-night salivary cortisol. Additionally, scalp-hair cortisol and cortisone analysis can detect long-term glucocorticoid excess and intermittent hypercortisolism, as seen in cyclical Cushing's syndrome.[7]

We report an unusual case of a male who presented with uncontrolled diabetes, polyuria, weight loss, and hyperpigmentation, and was found to have ectopic Cushing's syndrome.

CASE REPORT

A 24-year-old male presented with polyuria, polydipsia, and unintentional weight loss of 13 kg over 6 months. He reported hyperpigmentation of the face, knuckles, and oral mucosa for 6 months and two episodes of hemoptysis a month prior, for which he had received symptomatic treatment. No history of diabetic ketoacidosis, chronic abdominal pain, jaundice, or tuberculosis. No family history of diabetes or endocrine disorders. He denied alcohol, tobacco, or drug use. On examination, he was conscious and oriented. His vital signs were as follows: blood pressure (BP), 154/96 mmHg; heart rate (HR), 80 bpm; respiratory rate (RR) 18/min. He had a body mass index (BMI) of 19.6 kg/m^2. He had hyperpigmentation over the lips, buccal mucosa, knuckles, broad purple abdominal striae, proximal muscle weakness, Tinea infection over the forearm and the inguinal region (Figures 1 a-d).

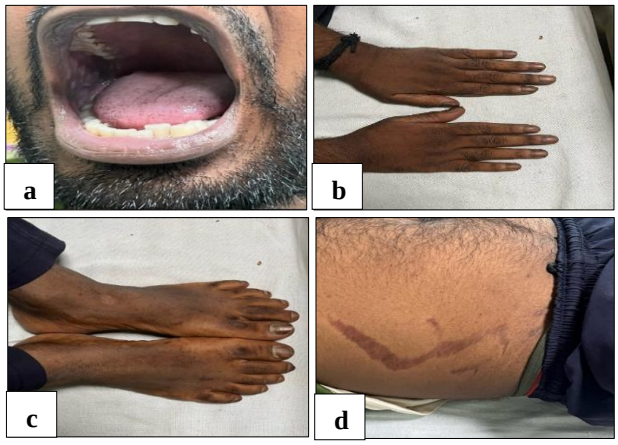

Figure 1: (a) Hyperpigmentation of lips and buccal mucosa, tongue, (b) knuckles, (c) feet, and (d) broad purple striae over abdomen.

Investigation showed serum cortisol (8 am): 82 mcg/dl (normal range 5-25 mcg/dl), midnight awake serum cortisol: 211 mcg/dl, overnight dexamethasone suppression test: 27.32 mcg/dl (normal <1.8 mcg/dl), plasma ACTH: 320 pg/ml (normal range 5-46 pg/ml), high-dose dexamethasone suppression test (HDDST): 16 mcg/dl (suppression 41%), fasting glucose: 278 mg/dl, serum sodium: 140 mg/dl (range-135-145 mg/dl), and serum potassium: 3.1 mg/dl (range 3-5-5.5 mg/dl).

HRCT chest showed multiple pulmonary nodules in bilateral lung fields, some attached to pleura; largest lesion 2.8×2.8 cm in right middle lobe, Ga-68 DOTANOC PET-CT revealed increased SSTR expression in bilateral lung nodules and some pleural nodules (SUV max 4.24). Magnetic resonance imaging (MRI) pituitary was normal (Figures 2a and b).

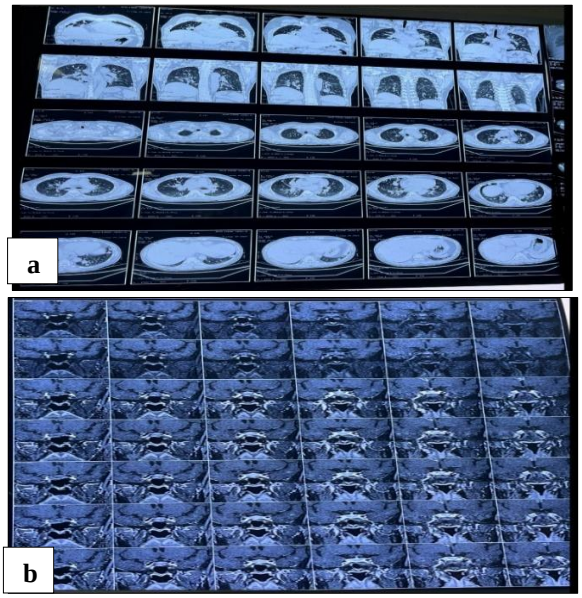

Figure 2: (a) HRCT chest showed multiple pulmonary nodules in bilateral lung fields, some attached to pleura; largest lesion 2.8×2.8 cm in right middle lobe, and (b) MRI showing normal pituitary gland.

Endobronchial biopsy confirmed atypical carcinoid tumor, grade 2, Ki-67 index: 4%, chromogranin A and synaptophysin positive.

The patient was started on ketoconazole 800 mg/day, potassium supplements, insulin for hyperglycemia, telmisartan 40 mg, and referred for surgical evaluation. However, as the patient was having extensive lung involvement, surgical resection was not feasible. Subsequently, he was treated with octreotide LAR (30 mg/month) and everolimus (10 mg/day) combination along with ketoconazole. Later, the patient developed pulmonary Koch's afterwards, and anti-tubercular therapy was also started. Patients showed some initial improvement in the form of a decrease in insulin requirement, a decrease in antihypertensive requirement. However, later on patient again deteriorated with significant weight loss and psychiatric manifestations, and urinary cortisol was also high despite therapy. So, he was

advised to undergo bilateral adrenalectomy for control of hypercortisolaemia. But the patient and relatives denied the same and were lost to follow-up.

DISCUSSION

Ectopic ACTH syndrome is an uncommon yet important differential diagnosis in patients presenting with hypercortisolism. In this case, the rapid progression of diabetes, significant weight loss, and marked hyperpigmentation raised suspicion for a systemic disorder. Hyperpigmentation occurs because of elevated ACTH levels, stimulating melanocortin receptors. The differential diagnosis included Cushing's disease due to pituitary adenoma, adrenal tumors, and ectopic ACTH production. Our patient had a normal pituitary, and HRCT chest showed multiple nodules, which on biopsy came out to be atypical carcinoid.

Carcinoid tumors, known as slow-growing neuroendocrine tumors, account for a subset of ectopic ACTH-producing neoplasms; approximately 10–20% of bronchial carcinoids secrete ACTH.[8] Among these, atypical carcinoids demonstrate higher mitotic activity and greater metastatic potential compared to typical carcinoids, as defined by the WHO 2019 classification.

Accurate localization of the ectopic ACTH source is essential for targeted management. Ga-68 DOTANOC PET-CT scanning has emerged as the gold standard for detecting neuroendocrine tumors due to its high sensitivity for somatostatin receptor expression.[9] In this patient, imaging revealed multiple lung lesions and mediastinal lymph node involvement, indicating advanced disease.

Management of ectopic ACTH syndrome involves a multidisciplinary approach. Initial treatment aims at medical control of hypercortisolism with agents such as ketoconazole, metyrapone, or mifepristone. Definitive therapy includes surgical resection of the primary tumor, and in refractory cases, bilateral adrenalectomy may be considered. For patients with metastatic disease, somatostatin analogs and targeted radionuclide therapy can be utilized. Prognosis largely depends on the tumor's degree of differentiation, Ki-67 proliferation index, and extent of metastases. Specifically, atypical carcinoids have a more malignant behaviour with significantly lower 5- and 10-year survival rates of 50–95% and 38–75%, respectively.[10]

This case highlights key clinical lessons: young patients presenting with rapidly progressive diabetes and hyperpigmentation should undergo prompt endocrine evaluation; persistent metabolic instability despite standard treatment warrants a hormonal work-up; and early involvement of a multidisciplinary team is critical to optimise patient outcomes.

CONCLUSION

This case emphasises the need for high clinical suspicion for ectopic ACTH syndrome in young patients with rapid-onset diabetes and systemic features. Early diagnosis and a multidisciplinary treatment plan are crucial to improving outcomes.

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