Severe Hypercortisolism with Hypokalemic Alkalosis Mimicking Ectopic Cushing Syndrome in a Patient with Cushing Disease Due to Pituitary Microadenoma

Sir,

Endogenous Cushing syndrome (CS) is a clinical state resulting from prolonged, inappropriate exposure to excessive endogenous glucocorticoid secretion and is characterized by loss of normal feedback mechanism of the hypothalamic–pituitary–adrenal (HPA) axis and the normal circadian rhythm of glucocorticoid secretion. Adrenocorticotropic hormone (ACTH)-dependent form (pituitary/ectopic source) accounts for about 85–90% of all cases of endogenous CS.[1] Unlike Cushing disease (CD), ectopic CS is more common in males and classically presents with short duration of symptoms, rapid weight loss, edema, profound muscle weakness, hyperpigmentation, hypokalemic alkalosis and metabolic features of severe hypercortisolism. However, this demarcation may not always hold true and a significant overlap between these two conditions may be seen in the clinical practice. A stepwise and meticulous investigative approach may help unveil the correct diagnosis in such cases.[2-3]

A 32-year-old married female presented to us with 6 months history of oligomenorrhea, hirsuitism, and acneiform eruptions over the face. She also noted rounding of the face, difficulty in getting up from squatting position, and development of broad ecchymotic patches at the sites of blunt trauma/venipuncture over the same duration. She did not notice any new striae over the abdomen; however, the striae from previous pregnancy had become increasingly dehiscent and pinkish over the past 6–8 months. During the past 1 year, she had documented unintentional weight loss of about 8 kg and had become increasingly irritable and withdrawn. On questioning, she gave history of hyperpigmentation over the knuckles and nail bed of fingers and toes. She was also detected to have diabetes mellitus and hypertension 1 month back, both of which were poorly controlled at the time of presentation. There was no history of headache, field defects, galactorrhea, flushing, diarrhea, cough, or wheezing. On examination, blood pressure was 154/100 mmHg and heart

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Letters to the Editor

Table 1: Baseline investigations of the patient

| Parameter                      | Value  | Normal          |
|--------------------------------|--------|-----------------|
| Hemoglobin (g/dL)              | 13.5   | 12-15           |
| Urea/Creatinine (mg/dL)        | 29/0.6 | 20-40/0.5-1.4   |
| Calcium/Phosphorous (mg/dL)    | 9.0/3.7| 8.5-10.4/2.5-4.5|
| Sodium/Potassium (meq/L)       | 145/2.8| 135-145/3.5-5.5 |
| Bicarbonate (meq/L)            | 33     | 22-26           |
| SGOT/SGPT/ALP (IU/L)           | 76/341/273 | <40/40/80-240 |
| Glycated hemoglobin (%)        | 7.5    | <5.7            |
| Fasting plasma glucose (mg/dL) | 164    | <100            |
| Total cholesterol/Triglyceride (mg/dL) | 142/218 | <200/<150 |
| LDL/HDL cholesterol (mg/dL)    | 54/44  | <100/>50        |
| Free T4 (ng/dL)                | 1.59   | 0.93-1.7        |
| TSH (µIU/mL)                   | 1.61   | 0.27-4.2        |
| LH/FSH (mIU/mL)                | <0.1/0.62 | 2.4-12.6/3.5-12.5 |
| Testosterone (ng/mL)           | 0.927  | 0.08-0.48       |
| DHEAS (µg/dL)                  | 528.5  | 98-340          |
| Prolactin (ng/mL)              | 6.45   | 6.0-29.9        |
| 8 AM serum cortisol (µg/dL)    | 51.4, 61.3 | 6.2-19.4   |
| 11 PM serum cortisol (µg/dL)   | 37.5, 46.2 | <7.5   |
| 11 PM salivary cortisol (µg/dL)| 2.3, 3.7  | <0.43           |
| LDDST cortisol (µg/dL)         | 45.73  | <1.8            |
| ACTH (pg/mL)                   | 153.5, 247.8 | 7.2-63.3 |
| HDDST cortisol (µg/dL)         | 22.63 (>50% suppression) | >50% suppression suggests pituitary source |
| CRH-IJV test (100 µg IV CRH)   |        | Ratio>1.6, ACTH rise ≥50%, and cortisol rise ≥13% suggests pituitary source |
| 3-min Rt IJV:periphery ACTH ratio | 2.26   |                  |
| 5-min Lt IJV:periphery ACTH ratio | >2.27  |                  |
| % ACTH rise during the test    | 570.6  |                  |
| % Cortisol rise during the test| 20.0   |                  |

TSH: Thyroid stimulating hormone, LH: Leuteinizing hormone, FSH: Follicle stimulating hormone, DHEAS: Dehydroepiandrosterone sulfate, LDDST: Low-dose dexamethasone suppression test, ACTH: Adrenocorticotropic hormone, HDDST: High-dose dexamethasone suppression test, CRH-IJV: Corticotropin releasing hormone-internal jugular vein

Figure 1: Clinical photograph showing moon facies, increased facial hair, acneiform eruptions, and ecchymotic patches over both forearms.

Figure 2: MRI sella (sagittal and coronal views) showing 8 mm pituitary microadenoma (arrow).

rate was 102 beats/min. Her weight, height, and body mass index were 58 kg, 149 cm, and 26.3 kg/m², respectively. She had moon facies, prominent dorsocervical fat pad, thin skin, broad ecchymotic patches over forearm and arm, wide (>1 cm) dehiscent pink striae over abdomen and proximal myopathy involving both lower limbs [Figure 1]. Grade II acanthosis nigricans, facial hirsutism, and acneiform eruptions over the face were also noted. No back deformity or bony tenderness was found.

Her investigations were significant for the presence of transaminitis, hypokalemia, metabolic alkalosis, hyperglycemia, androgen excess, and ACTH-dependent hypercortisolism [Table 1]. Fundus examination revealed grade II hypertensive retinopathy. Next, we proceeded with the tests to delineate the etiology of ACTH-dependent hypercortisolism. Serum cortisol suppression (>50%) on high-dose dexamethasone suppression test (HDDST), positive
ACTH and cortisol response on peripheral corticotrophin releasing hormone (CRH) stimulation (≥50% and ≥13% rise, respectively) and positive CRH-stimulated internal jugular vein (IJV):peripheral ACTH gradient [4] (ratio >1.6) suggested a possibility of pituitary source of ACTH production [Table 1]. Magnetic resonance imaging (MRI) of sella revealed a 8-mm pituitary microadenoma [Figure 2]. Computed tomography (CT) of chest and abdomen and Ga-68 DOTANOC PET/CT done to exclude the ectopic source were normal except for the presence of bilateral adrenal hyperplasia.

She underwent excision of the pituitary adenoma by endoscopic transnasal transsphenoidal surgery. Preoperatively, glycemic control was optimized using multiple subcutaneous insulin injection (MSII) and blood pressure/potassium controlled using a combination of oral potassium supplements, spironolactone, amlodipine, and telmesartan. On postoperative day 2, morning serum cortisol was documented to be 3.4 µg/dL, following which she was initiated on oral prednisolone. She was discharged on postoperative day 7 on following medications – oral prednisolone 7.5 mg/day, MSII (about 50% of preoperative insulin dose), and antihypertensive drugs (amlodipine and telmesartan at 50% of preoperative dose). Histopathology confirmed a pituitary adenoma with positive immunohistochemical staining for ACTH and MIB-1 index (cell proliferation marker) of 1%. Her insulin and antihypertensive requirement decreased gradually, and by postoperative month 4, she could completely discontinue medications for both diabetes and hypertension. She was continued on oral prednisolone in follow-up visits, awaiting recovery of the HPA axis, and the dose was gradually reduced to 2.5 mg/day [Table 2]. By postoperative month 6, she reported improvement in mood, fading of striae, improvement in abnormal fat distribution, and resumption of regular menstrual cycles. At a recent visit (postoperative month 12), she continued to remain in clinical and biochemical remission with persistent requirement of oral glucocorticoid.

Our patient presented with several clinical features to suggest ectopic CS – short duration of symptoms, weight loss, hypokalemic alkalosis, proximal myopathy, hyperpigmentation, markedly elevated ACTH levels, and severe hypercortisolism. However, various investigations directed at the etiology of ACTH-dependent CS (MRI sella, HDDST, and CRH-IJV test) suggested a possibility of CD due to pituitary microadenoma. She had a successful adenoma resection and continues to remain in clinical and biochemical remission till date.

Hypokalemia is believed to be an important discriminator between the two forms of ACTH-dependent CS; however, up to 10% of patients with CD may exhibit low potassium levels. Hypokalemia occurs due to overwhelming of the enzyme 11-beta-hydroxysteroid dehydrogenase by excessive circulating cortisol, resulting in inappropriate activation of the mineralocorticoid receptor. [1] Therefore, hypokalemia is actually representative of the severity of hypercortisolism and is not specific for the etiology of CS. In a large series of 64 patients with ACTH-dependent CS (ectopic, n = 16; CD, n = 48), spontaneous hypokalemia was seen in all patients (100%) with ectopic CS and 4 patients (8.3%) with CD. [3]

We have presented this case for its atypical clinical presentation and to emphasize the importance of a stepwise and meticulous approach to diagnosis in such patients.

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**Conflicts of interest**
There are no conflicts of interest.

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