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Case Report

A 36-Year-Old Woman With an Unexpected Cause of Hypokalemia

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Abstract

A 36-year-old woman complained of bilateral lower limb weakness for the last 3 days. She could move her upper limb, neck, and facial muscles and had no respiratory or swallowing difficulties. About 4 years ago, she complained of sudden weakness involving her lower limbs. Two years later, she had another episode involving only the right upper limb. In both cases, she was hypokalemic and received oral and intravenous potassium. She is a known diabetic and has polycystic ovary disease. Her blood pressure was 150/100 mm Hg, and body mass index was 29. Her serum potassium was 2 mEq/L, plasma renin 5 ng/dL, plasma aldosterone 0.63 µIU/mL, and aldosterone to plasma renin activity ratio 8. Cushing syndrome was considered a possibility. Subsequent analysis indicated a baseline cortisol level of 19.6 µg/dL at 8 AM. A screening overnight 1-mg dexamethasone suppression test (DST) showed 17 µg/dL cortisol. The low-dose DST revealed a cortisol level of 10.8 µg/dL. Adrenocorticotropin level was 196 pg/mL, and 24-hour urinary cortisol level was 1284 mg/dL. A high dose of 8-mg DST at 11 PM to find the source of hypercortisolism performed yielded 15.9 µg/dL. Magnetic resonance imaging of the pituitary displayed a well-defined, heterogeneously enhanced mass lesion (15 × 13 × 11 mm) in the sella with mild suprasellar extension. Transsphenoidal resection and stereotactic radiosurgery were performed on the tumor with hormone replacement and glycemic control following surgery.

Key Words: hypokalemia, Cushing syndrome, pituitary macroadenoma

Abbreviations: ACTH, adrenocorticothrophin hormone; BMI, body mass index; CS, Cushing syndrome; DST, dexamethasone suppression test; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; HSD, 11β hydroxysteroid dehydrogenase; MRI, magnetic resonance imaging; OHA, oral hypoglycemic agent.

Introduction

Cushing syndrome (CS) is a condition that is due to endogenous/exogenous hypercortisolism. Cushing disease is termed explicitly for the hypersecretion of adrenocorticothrophin hormone (ACTH) by an ACTH-secreting pituitary adenoma. The prevalence of Cushing disease is 40:1 000 000, with a female predilection (female:male = 9:1). Of all pituitary adenomas, functional and nonfunctional, the ACTH-secreting adenoma represents about 10% to 12% [1]. Endogenous CS may be ACTH dependent (pituitary tumor or ectopic ACTH production) or ACTH independent secondary to excess cortisol secretion from adrenal glands. It is crucial to consider several conditions associated with a pseudo-Cushing state when evaluating patients for CS. Some are pregnancy, morbid obesity, severe psychological stress (including major depressive disorder), uncontrolled diabetes mellitus, chronic alcoholism, and severe sleep apnea [2].

This case report is of a patient presenting with symptomatic refractory hypokalemia with episodes of limb weakness. She exhibited features of metabolic syndrome (obesity, high blood pressure, high blood triglycerides, low high-density lipoprotein (HDL) cholesterol, and insulin resistance) and polycystic ovary disease. On investigating, an ACTH-dependent pituitary macroadenoma was noted.

CS/Cushing disease, as a differential diagnosis, should be considered in the presence of refractory hypokalemia.

Case Presentation

A 36-year-old woman came to the outpatient department complaining of bilateral lower limb weakness for the last 3 days. She could move her upper limb, neck, and facial muscles and had no respiratory or swallowing difficulties. About 4 years ago, she complained of sudden weakness involving her lower limbs. Two years later, she had another episode involving only the right upper limb. In both cases, she was hypokalemic and received oral and intravenous potassium, but the cause remained uncertain. There was a strong family history of diabetes. She was diagnosed with polycystic ovary disease, hypertension, dyslipidemia, and diabetes mellitus 4 years back when she presented with irregular menses to the gynecologist. Her medications included oral hypoglycemic agents (OHAs)—metformin, voglibose, glimepiride—and oral contraceptive pills. Her glycemic control remained refractory to the highest OHA doses. There was no history of recent or chronic vomiting or diarrhea. She did not experience any thyrotoxicosis symptoms and was not taking β-adrenergic agonists. The patient was not on diuretics or corticosteroids. She did not

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Figure 1. Image showing hyperpigmentation of the knuckles and dorsum of both hands.

consume excessive licorice. There was no notable family or personal history of autoimmune disorders, such as Sjögren syndrome or systemic lupus erythematosus, that could result in renal tubular acidosis.

Diagnostic Assessment

On examination, the patient was obese, with a body mass index (BMI) of 29.0 (according to World Health Organization Asia Pacific BMI standards) and a blood pressure of 150/100 mm Hg. Her physical examination revealed androgenic alopecia and acanthosis nigricans around the neck, with mild knuckle pigmentation. No striae, prominent dorsocervical fat pad, or moon face were present at her initial presentation. However, 2 months later, she showed marked hyperpigmentation in the knuckles (Fig. 1), around the mouth, and periorbital regions (Fig. 2). Acanthosis nigricans had deepened, and a prominent dorsocervical fat pad (buffalo hump) was documented (Fig. 3). Listed in Table 1 are the patient's initial laboratory values.

At this point, CS was considered a possibility. Further evaluation showed a baseline 8 AM cortisol of 19.62 µg/dL or 541.3 nmol/L. (5-23 µg/dL or 138-635 nmol/L). A 1-mg screening overnight dexamethasone suppression test (DST) showed a value of 17.6 µg/dL or 485.6 nmol/L (normal = <1.8 µg/dL or 49.6 nmol/L). As this was positive for CS, a confirmatory 0.5-mg low dose DST (0.5 mg every 6 hours for 48 hours) was conducted. On the third day, at 8 AM, serum cortisol level was measured as 10.8 µg/dL or 298 nmol/L (normal = <1.8 µg/dL or 49.6 nmol/L). Her ACTH level was 196 pg/mL, and 24-hour urinary cortisol level 1284 mg/dL.

A high-dose 8-mg overnight DST was performed to differentiate between pituitary and ectopic Cushing. Repeated baseline serum cortisol levels showed a value of 24 µg/dL or 662 nmol/L. After the suppression, the obtained cortisol level was 15.9 µg/dL or 438.6 nmol/L (normal suppression >50%).

Magnetic resonance imaging (MRI) of the pituitary gland revealed a well-defined, heterogeneously enhancing mass lesion (measuring $15 \times 13 \times 11$ mm) in the sella with mild suprasellar extension. A widened sella was noted. Superiorly, the mass extended up to the optic chiasma. Laterally, the mass abutted the bilateral cavernous sinuses without intra-sinus extension. (Figs. 4 and 5).

The diagnosis was Cushing disease—ACTH-producing pituitary macroadenoma with mild suprasellar extension with no compressive features.

Treatment

The patient's medications included insulin (basal-bolus regimen), Tablet (T.) thyroxine 50 mcg once a day, T. metformin 500 mg twice a day, oral potassium supplements, and antihypertensive (T. telmisartan 40 mg) before the surgery. The patient underwent endoscopic transnasal transsphenoidal resection of the lesion. Immunostaining of the tumor tested positive for ACTH. After 4 months, a repeat MRI of the pituitary showed residual adenoma tissue, and thus she underwent Gamma Knife radiation (stereotactic radiosurgery).

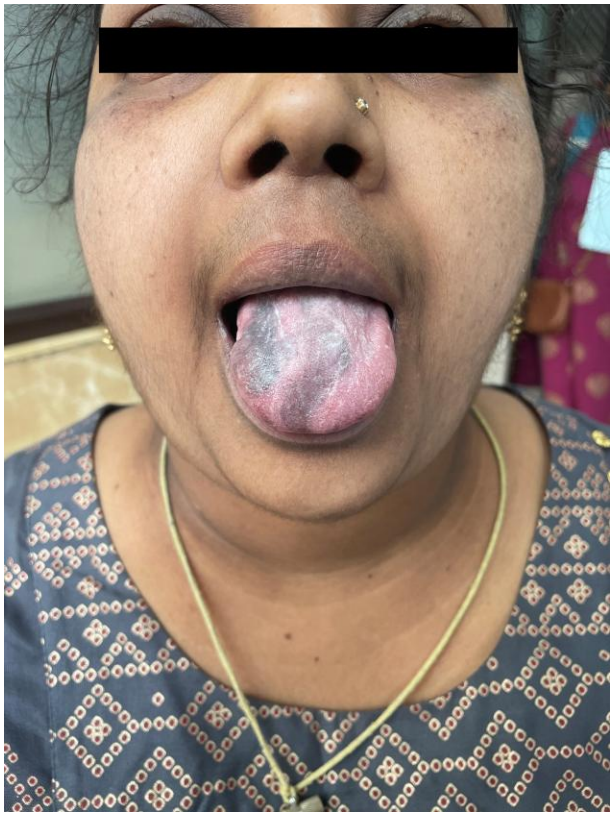

Figure 2. Image showing periorbital, circumoral, and mucosal (tongue) hyperpigmentation. Note acanthosis nigricans around the neck.

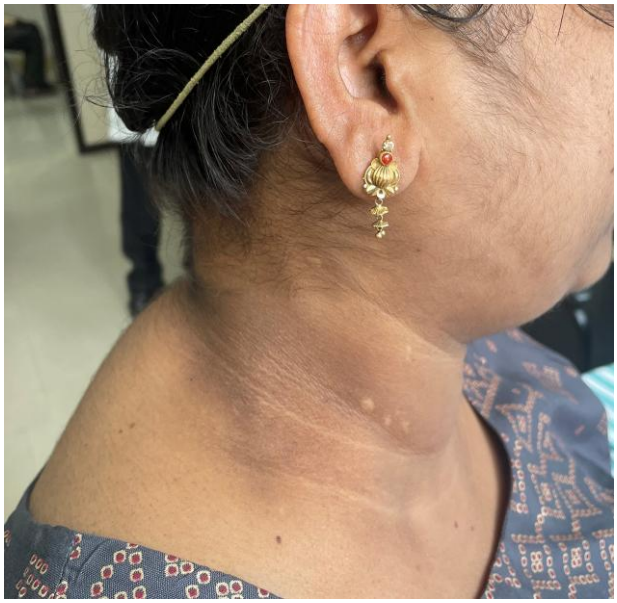

Figure 3. Image showing acanthosis nigricans around the neck and buffalo hump, which developed later in the course of the disease, before surgery.

Outcome and Follow-up

There were no complications post surgery, and the patient had no more hypokalemia episodes. Hyperpigmentation significantly reduced. Following surgery, the patient lost 10 kg and has achieved adequate glycemic control. Her postoperative medication included steroids (T. prednisolone 10 mg, in tapering doses), thyroxine, insulin + OHAs, and oral contraceptive pills. The patient was taken off potassium supplements and antihypertensives at 6 months' follow-up.

Table 1. Initial Laboratory Values

Variables	Value	Reference Range
BLOOD PARAMETERS		
Serum Potassium	2.0 mmol/L (2.0 mEq/L)	3.5-5.5 mmol/L (3.5-5.5 mEq/L)
Serum Bicarbonate	26.2 mmol/L (26.2 mEq/L)	19-31 mmol/L (19-31 mEq/L)
Serum Magnesium	0.62 mmol/L (1.5 mg/dl)	0.85 - 1.1 mmol/L (1.5 – 2.5 mg/dl)
pH	7.49	7.35-7.45
Triglyceride level {In female}	3.45 mmol/L (305 mg/dl)	0.45 – 1.58 mmol/L (40-140 mg/dl)
HDL level {In female}	30 mg/dl (0.77 mmol/L)	42-88 mg/dl (1.1-2.27 mmol/L)
HbA1C (HPLC method)	12.3	(<5.6 – normal; 5.7-6.4 – pre diabetic; > 6.5 – diabetes)
Plasma Renin Concentration	5.09 ng/dl	(2.52-39.2 ng/dl upright posture)
Plasma Aldosterone	0.63 µIU/ml	4.4-46.1 µIU/ml upright posture)
Aldosterone/Renin ratio	8.08	2–17 with a mean of 5.5
Serum ACTH level	43.1 pmol/L (196 pg/ml)	2.2 - 13.3 pmol/L (10-46 pg/ml)
URINARY PARAMETERS		
24-hour urinary potassium	21 mEq/day	<15 mEq/day
24 hr. urinary cortisol	3543.84 nmol/day (1284 µg/day)	9.66 - 124.2 nmol/day (3.5 - 45 µg/day)
Urinary potassium creatinine (K/Cr) ratio	2.9	< 1.5

ACTH: Adrenocorticotropic Hormone, HbA1C: Glycated Hemoglobin, HDL: High Density Lipoprotein

Discussion

Researchers propose specific mechanisms to explain the cause of hypokalemia in CS. The mineralocorticoid effect of cortisol is absent or minimal in typical situations as the enzyme 11β hydroxysteroid dehydrogenase (HSD) type 2 converts the excess cortisol to inactive cortisone.

At high cortisol levels, however, the enzyme may get overwhelmed, and mineralocorticoid effects may occur. A possible mutation or polymorphism in the 11β HSD type 2 gene may result in differences in the clinical expression of symptoms related to mineralocorticoid activity. Another possible explanation for the mineralocorticoid effect is the direct inhibition of the 11β HSD type 2 enzyme by high ACTH levels [3]. In our patient with Cushing disease, hypokalemia likely occurred because of the high levels of corticotrophin from the macroadenoma. Hypokalemia secondary to hypercortisolism is described more for ectopic CS than pituitary adenoma. Still, it does occur with an incidence of 10% [4].

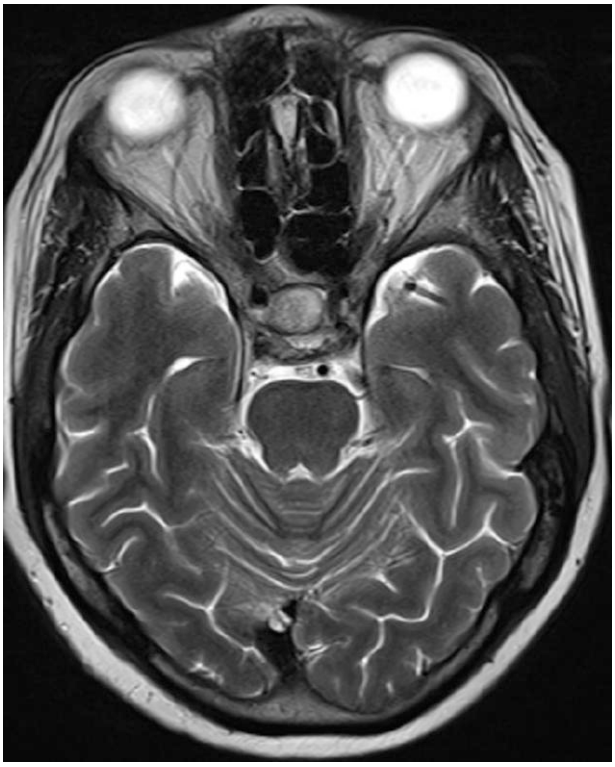

Figure 4. T2-weighted magnetic resonance imaging scan of the brain in a sagittal section, showing a well-defined heterogeneously enhancing mass lesion (measuring 15 × 13 × 11 mm) in the sella with mild suprasellar extension. The sella is widened.

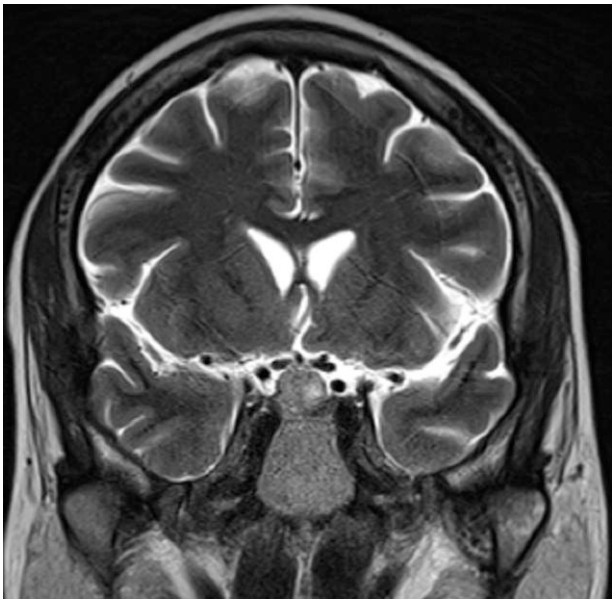

Figure 5. T2-weighted magnetic resonance imaging scan of the brain in a frontotemporal section, showing a well-defined heterogeneously enhancing mass lesion (measuring 15 × 13 × 11 mm) in the sella with mild suprasellar extension. The sella is widened.

The patient is still under our follow-up, with substantial improvement post treatment. This case is interesting as the patient presented with only features of hypokalemic paralysis and metabolic syndrome but did not have obvious clinical manifestations of CS.

Learning Points

- CS should be considered in the event of recurrent hypokalemia, even if there are no clinical symptoms of hypercortisolism.
- In suspicion of Cushing disease, a screening test, either 1-mg overnight DST or midnight salivary-free cortisol measurement, should be performed as it is inexpensive, convenient, and can be conducted on an outpatient basis. Overnight salivary cortisol estimation can be used as a screening technique for patients using OC pills because it measures free cortisol. A urinary free cortisol test can be used as a substitute if overnight salivary cortisol monitoring is unavailable.
- Despite increasing lifestyle disorders, hyperglycemia and hypertension might be caused by an underlying CS.

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Contributors

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

References

1. Buliman A, Tataranu LG, Paun DL, Mirica A, Dumitrache C. Cushing's disease: a multidisciplinary overview of the clinical features, diagnosis, and treatment. *J Med Life*. 2016;9(1):12-18.
2. Wehbeh L, Hamrahian AH. Cushing syndrome. *Johns Hopkins Diabetes Guide*. 2020. Accessed December 18, 2022. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Diabetes_Guide/547032/all/Cushing_Syndrome
3. Turgut S, Ilhan M, Soytas R, Alay M, Kazancioglu R. A rare entity in Cushing's disease: severe hypokalemia and metabolic alkalosis. *Med Sci Discov*. 2021;8(3):189-192.
4. Howlett TA, Drury PL, Perry L, *et al*. Diagnosis and management of ACTH dependent Cushing's syndrome: comparison of the features of ectopic and pituitary ACTH production. *Clin Endocrinol (Oxf)*. 1986;24(6):699-713.