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Refractory Hypokalemia Revealing Cushing's Syndrome and Persisting after Bilateral Adrenalectomy: A Case Report and Review of the Literature

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Abstract **Case Report**

Cushing's syndrome (CS), a rare endocrine disorder, is characterized by a diverse range of clinical manifestations due to prolonged exposure to excess glucocorticoids. CS can be divided into ACTH-dependent and ACTH-independent types, with varying degrees of clinical severity. Biochemical abnormalities, such as hypokalemia, are associated with CS, potentially resulting from the mineralocorticoid effects of cortisol. We present a unique case of Cushing's disease with a prominent and persistent feature of hypokalemia, even after a successful bilateral adrenalectomy. The patient's clinical presentation included sudden abdominal obesity, lumbago, polyuria, polydipsia, chronic constipation, muscle cramps, and profound weakness. Early diagnostic evaluation revealed severe hypokalemia requiring treatment. Despite bilateral adrenalectomy, hypokalemia persisted postoperatively, necessitating ongoing potassium supplementation. This case highlights the complex interplay of hormones in CS and the need for comprehensive clinical and biochemical assessments. Hypokalemia is prevalent in Cushing's syndrome (CS), typically resulting from renal potassium loss, influenced by cortisol's mineralocorticoid-like effects. Additionally, ACTH might inhibit 11β-HSD2, allowing cortisol to act as a mineralocorticoid. Persistent hypokalemia in our ACTH-dependent CS case, even after bilateral adrenalectomy, raises questions about the role of ACTH and 11β-HSD2. Further research is needed to clarify these mechanisms and their relationship with CS.

Keywords: Cushing's syndrome, hypokalemia, bilateral adrenalectomy, 11 beta-hydroxysteroid2, ACTH, hypercortisim.

INTRODUCTION

Cushing's syndrome (CS) is a rare endocrine disorder characterized by a diverse range of clinical manifestations resulting from prolonged exposure to excess glucocorticoids. The syndrome's presentation varies from subclinical to overt, depending on the duration and intensity of steroid overproduction, necessitating a comprehensive diagnostic process. CS is categorized into two main types: ACTH-dependent and ACTH-independent. ACTH-dependent CS cases primarily involve pituitary adenomas (Cushing's disease) or extra-pituitary tumors (ectopic ACTH syndrome), while ACTH-independent CS arises from adrenal abnormalities [11,12].

Biochemical alterations, such as hypokalemia, metabolic alkalosis, and hypernatremia, are associated with CS, possibly due to the mineralocorticoid effects of cortisol. While these changes often present with non-specific clinical features, hypokalemia is more frequent in ectopic ACTH syndrome cases, with an incidence of 57-100%. Patients with ectopic ACTH syndrome typically exhibit higher cortisol and ACTH levels than those with Cushing's disease, though the exact relationship between elevated hormone levels and hypokalemia remains uncertain [3].

We present a case of a patient with an unusual presentation of Cushing's disease (CD), in which hypokalemia was the primary indicator and persisted following a successful bilateral adrenalectomy.

CASE REPORT

A 34-year-old female patient with no significant medical history developed rapidly progressing symptoms over two months, including abdominal obesity, right-sided lower back pain, polyuria, polydipsia, chronic constipation, muscle cramps, and

profound fatigue, necessitating wheelchair use. Her primary care physician observed a blood glucose level of 3 g/L and an HbA1c of 12.8%, leading to concerns about Cushing's syndrome. Consequently, she was directed to our emergency department.

Clinical examination revealed a conscious, asthenic patient with high blood pressure (15/8 cmHg) and a blood glucose level of 6 g/L, along with ketonuria. She had an overweight BMI of 26.8 kg/m² and exhibited clinical signs of Cushing's syndrome, including central obesity, purple striae, leg muscle atrophy, facial erythrosis, hypogastric sensitivity, and a positive Giordano sign on the left side.

Initial blood tests showed severe hypokalemia (2mmol/L) and predominantly neutrophilic leukocytosis. The glomerular filtration rate was normal, but there was thyrotropin deficiency requiring L-thyroxine treatment. An ECG displayed flat T-waves, a normal QT interval, and no U waves or ST-segment depression. However, hypokalemia proved refractory, necessitating both intravenous and oral potassium chloride supplementation. A potassium-sparing diuretic (spironolactone) was introduced at a dose of 150 mg/day in combination with 5 mg/day ACE inhibitors.

Given the patient's clinical presentation, Cushing's syndrome was suspected early on and subsequently confirmed by diagnostic tests. The ACTH level was 44.60 ng/ml, indicating ACTH-dependent Cushing's syndrome (Table 1).

Table 1: Hormonal Assessment

Analyses	**Patients Results**
Minute braking with dexamethasone	47,21 ug/dl
Midnight cortisol	44,73 ug/dl
ACTH	44,60 ng/ml

Due to the severe and complicated nature of Cushing's syndrome, the patient was treated with oral ketoconazole. However, hepatic cytolytic side effects led to treatment cessation (Table 2).

Table 2: Liver function tests of the patient

	Before the initiation of ketoconazole	**Post-Ketoconazole Initiation Follow-Up**
AST (Aspartate Aminotransferase)	28ui/l	**186 (5xNormal)**
ALT (Alanine Aminotransferase)	25ui/l	**432(13xnormal)**
GGT(Gamma-Glutamyl Transferase)	-	**58.79(1.3xnormal)**
PAL (Alkaline Phosphatase)	-	**143(1.3xnormal)**
Bilirubin	-	8.31(Normal)

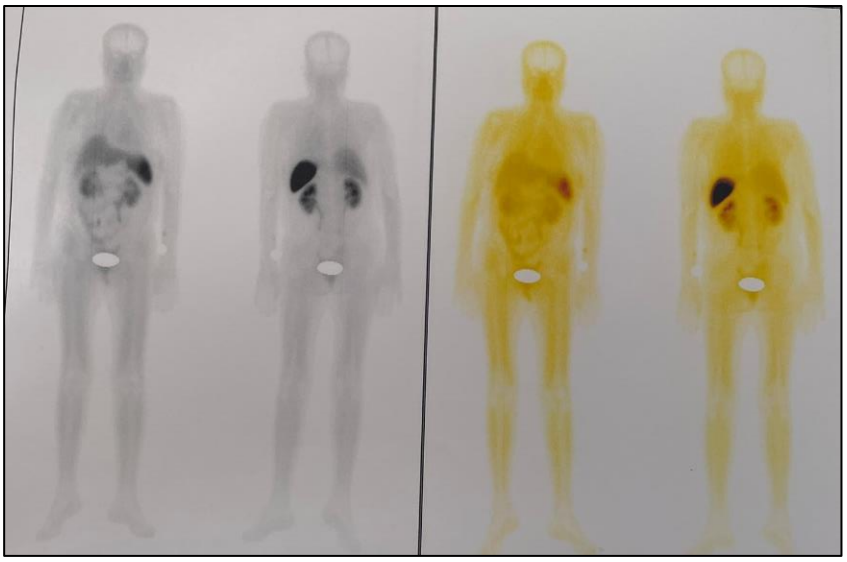

Figure 1: Results of our patient's Octreoscan

Imaging, including an MRI to assess the pituitary gland, returned normal results. Further evaluation for ectopic ACTH secretion via imaging and isotope tests uncovered a non-specific Flower's nodule. An Octreoscan (111 Pentetreotide) yielded negative results, indicating no somatostatin receptor overexpression in tumors, particularly in the lungs (Figure 1). A subsequent Hypothalamo-pituitary MRI

revealed a 4x2 mm microadenoma on the left side (Figure 2).

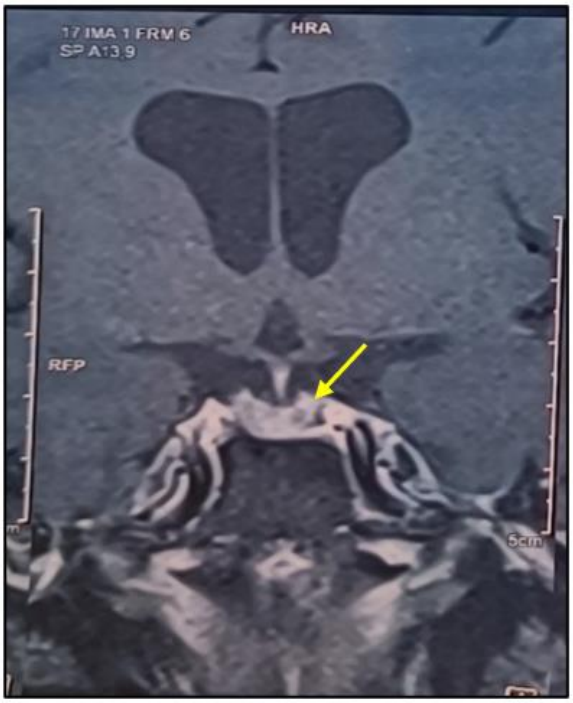

Figure 2: Hypothalamo-pituitary MRI showing a pituitary microadenoma

The patient underwent transsphenoidal surgery to remove the pituitary microadenoma. Postoperative complications included diabetes insipidus, requiring desmopressin. Corticosteroid therapy with hydrocortisone was initiated. Anatomopathological and immunohistochemical studies confirmed a pituitary adenoma expressing anti-ACTH antibodies.

Bilateral adrenalectomy was recommended due to the absence of improvement in Cushing's syndrome and persistent, unresponsive hypokalemia. Anatomopathological and immunohistochemical examinations supported the diagnosis of corticosurrenal hyperplasia with no signs of malignancy.

Despite the surgery, the patient continued to suffer from severe hypokalemia, with potassium levels as low as 2.2 mmol/L. However, her blood pressure and blood sugar levels returned to normal, allowing the discontinuation of insulin therapy and antihypertensive medications.

Table 3: Blood Electrolyte Profile of the Patient

	Preoperative	Postoperative
Sodium	145,3 mmol/l	145,61 mmol/l
Potassium	2 mmol/l	2,2 mmol/l

During her hospital stay, the patient was treated with hydrocortisone corticosteroids, L-thyroxine for thyroid deficiencies, sublingual desmopressin for diabetes insipidus, and oral supplements of vitamin D, iron, and potassium. Additionally, she received subcutaneous enoxaparin for thromboprophylaxis.

The patient's clinical condition improved, and her potassium levels normalized through oral supplementation.

DISCUSSION

Hypokalemia can be attributed to various factors, including reduced potassium intake, intracellular potassium redistribution, and increased potassium loss. Most cases of chronic hypokalemia are primarily linked to renal loss, with occasional cases related to excess mineralocorticoid activity. Many conditions associated with hyperreninemia can lead to secondary hyperaldosteronism and subsequent renal potassium loss. In rare cases, overproduction of adrenocorticotropic hormone (ACTH) can result in excessive renal potassium loss that exceeds normal levels [1, 2, 7].

We present a case of ACTH-dependent Cushing's syndrome (CS) with Cushing's disease as the underlying cause. The prominent and refractory hypokalemia is a key feature of our case. Importantly, this hypokalemia persisted even after bilateral adrenalectomy, making it an atypical presentation. Therefore, the presence of severe hypokalemia should raise suspicions of hypercortisolism, particularly when other potential causes have been ruled out.

Studies by Torpy *et al.*, have shown that hypokalemia is significantly more associated with ectopic CS compared to other causes of CS, affecting 57% of patients. Giraldi *et al.*, found an independent association between hypokalemia and 24-hour urine cortisol levels in patients with Cushing's disease. Similarly, Titan *et al.*, reported deep hypokalemia and metabolic alkalosis in a patient with ectopic adrenocorticotropic hormone syndrome, suggesting possible mechanisms. These findings emphasize the importance of considering severe hypokalemia not only in CS patients but also in those with Cushing's disease [4, 9].

The mechanisms underlying hypokalemia in CS are not yet fully understood. High cortisol levels, with in vitro binding affinity to the mineralocorticoid receptor (MR) similar to aldosterone, may lead to a mineralocorticoid-like effect. In a normal context, this effect is negligible due to the presence of the 11 beta-hydroxysteroid dehydrogenase 2 (11β-HSD2) enzyme, which converts cortisol into inactive cortisone. However, elevated cortisol levels can saturate 11β-HSD2, allowing mineralocorticoid effects to manifest. Mutations in the 11β-HSD2 gene can also result in cortisol overstimulating MR, causing renal sodium retention, hypokalemia, and reduced plasma renin and aldosterone secretion [8-11].

There were some articles reporting that ACTH itself could inhibit 11β-HSD2 activity.13–16 Those studies found that infusion of exogenous ACTH did not increase plasma cortisone concentrations despite a rise in cortisol. Thus, the high levels of ACTH in ectopic ACTH syndrome may inhibit 11β-HSD2, and thereby allow cortisol to act as a mineralocorticoid [13, 14].

Bilateral adrenalectomy was performed on our patient due to uncontrolled Cushing's syndrome, with the persistence of complications and the onset of side effects from medical treatment. However, hypokalemia persisted after bilateral adrenalectomy, thus reinforcing the hypothesis of the potential inhibition of the enzyme 11β-HSD2 by ACTH.

Further research is required to fully elucidate the role of the 11β-HSD2 gene and its relationship with the biochemical and clinical features of CS.

CONCLUSION

This case report serves as a reminder of the intricate interplay between hormones and the various manifestations of CS, emphasizing the need for comprehensive clinical and biochemical evaluations in the diagnostic process. Further research is essential to fully elucidate the underlying mechanisms of hypokalemia in the context of Cushing's syndrome, allowing for improved patient care and treatment strategies.

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