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A Rare Entity in Cushing's Disease: Severe Hypokalemia and Metabolic Alkalosis

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ABSTRACT

Objective: This case report aimed to highlight the prominence of considering Cushing's disease (CD) in the differential diagnosis of severe hypokalemia and metabolic alkalosis.

Case Report: A 63-year-old woman who was admitted to the emergency room with fatigue and severe weakness of extremities. Biochemistry results indicated severe hypokalemia (potassium = 1.2 mmol/L) and metabolic alkalosis (pH = 7.83) and based on further endocrinological investigations, the final diagnosis of CD was confirmed, and magnetic resonance imaging revealed a microadenoma in the right side of the pituitary gland. Transsphenoidal surgery was performed. After surgery, biochemical assessments showed normal potassium levels and corrected metabolic alkalosis without any further treatment. The hypothalamic–pituitary–adrenal axis recovered in nearly eight months and the patient was in remission.

Conclusions: Although hypokalemia could be present in CD, none of the previous studies have reported hypokalemia as severe as in this case. This case report highlighted the prominence of considering CD in the differential diagnosis of severe hypokalemia and metabolic alkalosis that could be a crucial part of biochemical features in CD.

Keywords: Cushing's Disease, Hypokalemia, Metabolic Alkalosis

INTRODUCTION

Cushing's syndrome (CS) is an endocrine disease characterized by chronic exposure to glucocorticoids and the most common reason for CS is therapeutic administration of exogenous glucocorticoids (1). ACTH-dependent CS (ADCS) is mostly caused by a pituitary corticotrope adenoma [Cushing's disease (CD)] in approximately 80% of cases, and less frequently by an extra pituitary tumor (ectopic ACTH syndrome). In addition to that, CS may be ACTH independent (AICS) when it is caused by excess production of cortisol by unilateral adrenocortical tumors or by bilateral surrenal hyperplasia or dysplasia (2). CS can precipitate several biochemical alterations such as hypokalemia, metabolic alkalosis, and hypernatremia, this may be caused by mineralocorticoid effects of cortisol. However, these alterations caused nonspecific clinical findings and their role in CD is still matter of debate. Hypokalemia and metabolic alkalosis are found rarely in CD although it is present 57% in ectopic ACTH syndrome (3). Previous limited studies have suggested that many patients with AICS are associated with hypokalemia and metabolic alkalosis, there are a few numbers of cases reported with hypokalemia and metabolic alkalosis in CD (4-7). The patient presented here is an unusual case of CD in which severe hypokalemia and metabolic alkalosis were the presenting findings.

CASE REPORT

A 63-year-old woman was admitted to the emergency room with a two-week history of fatigue, severe weakness of the lower and upper extremities, mild hypertension, and confusion.

Case Report

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Her medical history consisted of hypertension well controlled with perindopril and indapamide. She was diagnosed with type 2 diabetes mellitus (Hba1c 11.2%) 4 months ago and treated with metformin 1000 mg twice daily, insulin glargine 24 units plus insulin aspart 8 units with meals three times daily. She was a non-smoker and non-drinker, and her family history was insignificant.

Her physical examination revealed facial puffiness with plethora, petechiae over her abdomen, purple striae on the inner surfaces of the upper arms and obesity with a protuberant abdomen. Blood pressure was 150/90 mmHg with a pulse rate of 82/min respiratory rate was 10/min, and the temperature was 37.1oC in the supine position. The patient was 162.3 cm tall and weighed 76 kg. Neurological findings showed that she was confused without a sign of lateralization or focalization. Initial biochemistry results indicated severe hypokalemia and metabolic alkalosis (Table 1).

Table 1: Initial Biochemical Parameters

	Plasma value	Reference Range
Na (mmol/L)	136	136-145
Cl (mmol/L)	70	98-107
K (mmol/L)	1.2	3.5-5.1
Glucose (mg/dL)	234	70-100
Creatinine (mg/dL)	0.8	0.5-0.9
Urea (mg/dL)	50	10-50
Leukocyte (x10^3/µL)	7.9	3.8-10
Hemoglobin (gr/dL)	11.6	11.5-15.5
Platelet (x10^3/µL)	205	150-400
pH	7.83	7.35-7.45
PCO_2 (mmHg)	57.2	32-45
PO_2 (mmHg)	77	75-100
SaO_2 (%)	97.9	95-100
HCO_3 (mmol/L)	68.1	24-28
C-reactive protein (mg/dL)	0.2	0-0.5

CS was suspected and endocrinological investigations (urinary free cortisol, 1 mg, and 2 days 2 mg dexamethasone suppression test) showed ACTH-dependent hypercortisolism and 8 mg dexamethasone suppression test indicated a pituitary origin of ACTH secretion (Table 2).

Pelvis, chest, and abdomen CTs were insignificant. Bilateral inferior petrosal sinus sampling (BIPSS) showed a maximal central / peripheral plasma ACTH ratio of 2.1 before and 3.7 after the intravenous administration of Corticotrophin-releasing hormone (CRH) 100 µg, also showed a significant right to the left gradient of 14.9 times (higher on right side). Magnetic resonance imaging (MRI) of the pituitary gland determined a 7 mm x 5 mm the late enhancement area in the right side.

Imaging assessment confirmed that the patient has a pituitary microadenoma without any symptoms by local mass effect. She underwent transsphenoidal surgery (TSS) with 300 mg hydrocortisone infusion and the histological findings were consistent with a pituitary adenoma. Immunohistochemistry showed strong positivity with ACTH and revealed weak immunostaining for prolactin, follicle-stimulating hormone also p53 stain shows rare positivity and Ki-67 was 2% (Figure 1).

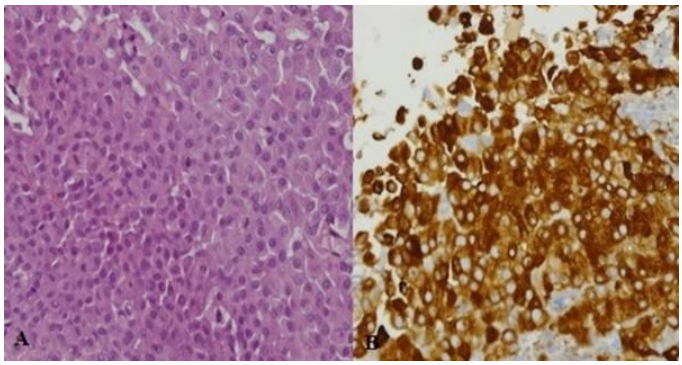

Figure 1 A) Pituitary adenoma stained with H&E (X200) **B)** ACTH immunostaining of the pituitary adenoma (X200), heavy brown staining of cells indicating ACTH production.

After surgery, hormonal evaluation verified the lack of hypercortisolism, and biochemical assessments showed normal potassium levels and corrected metabolic alkalosis without any further treatment for these conditions (Table 2). Postoperative early cortisol level was 1.7 µg/dL and patient received 5mg/day prednisolone treatment after surgery. In follow-up examinations, the hypothalamic–pituitary–adrenal axis recovered in nearly eight months and prednisolone treatment was stopped. Plasma cortisol level was suppressed to 0.9 µg/dL with 1mg dexamethasone suppression test and the patient was in remission.

Table 2: Initial and Follow-up Endocrinological and Biochemical Parameters

	Initial	Pre-op*	Post-op	Reference Range
Plasma Active Renin (uIU/ml)	28.1	-	-	4.2-69.7
Plasma Aldosterone (ng/dL)	3.8	-	-	3.7-31
Serum Cortisol (µg/dL)	67.7	36.7	1.7	4.6-22.8
Urinary free cortisol (µg/24h)	3846.4	-	-	36-137
Plasma ACTH (pg/mL)	133	89.2	38.6	7.2-63.3
Serum cortisol after 1 mg dexamethasone (µg/dL)	6.98	-	-	<1.8
Serum cortisol after 2 mg dexamethasone (µg/dL)	10.3	-	-	<1.8
Serum cortisol after 8 mg dexamethasone (µg/dL)	37 (55%suppression)	-	-	**
Ph	7.83	7.76	7.42	7.35-7.45
HCO_3 (mmol/L)	68.1	62.2	27.4	24-28
K (mmol/L)	1.2	2.6	3.6	3.5-5.1

ACTH: Adrenocorticotropic hormone, * Patient received intravenous administration of 10 mEq/h potassium chloride infusions and oral potassium chloride (40 mEq/8 h.), **Suppression of plasma cortisol by at least 50% indicates Cushing's Disease

DISCUSSION

CD is a rare endocrine disorder caused by ACTH-secreting pituitary tumors with an incidence of 80-85% in all patients with ADCS. The major manifestations of CS are centripetal obesity, facial plethora, skin atrophy and wide purplish striae, proximal muscle weakness, glucose intolerance, hypertension, and psychological changes (2). After performing initial diagnostic tests for CD, BIPSS is the most accurate test for diagnosing and lateralization, with a sensitivity of up to 97% and specificity of up to 100% when CRH stimulation is used (8). We performed BIPSS which showed a significant right to left gradient and MRI revealed a microadenoma in the right side of the pituitary. Successful TSS was performed to the patient and treatment was achieved.

The main point of this case was severe hypokalemia and metabolic alkalosis, despite these are more expected findings in ectopic CS than CD. Torpy et al. identified 58 patients with ectopic CS in a retrospective case review and they showed hypokalemia was much more related with ectopic CS than in patients with other causes of CS, affecting 57% of patients. Additionally, they found a significant relationship with 24-hour urine cortisol excretion and the presence of hypokalemia (3). Giraldi et al. evaluated gender-related differences in the presentation of CD, as regards biochemical results of hypercortisolism, and found hypokalemia was independently associated with 24-hour urine cortisol levels (9). Titan et al. have reported deep hypokalemia and metabolic alcoholics in a patient with ectopic adrenocorticotropic hormone syndrome and have suggested possible mechanisms (10). Consistent with this finding, 24-hour urine cortisol level was elevated to 30 times normal values in our patient with severe hypokalemia. To our knowledge, none of the previous studies have reported hypokalemia as severe as in our patient. This finding suggests that severe hypokalemia should be considered not only in patients with CS but also in patients with CD.

Plausible mechanisms have been postulated to explain the reasons of hypokalemia and metabolic alkalosis in CS. The influence of CS on these biochemical alterations and pathological mechanisms involved are still not clarified. High cortisol concentration which has an in vitro binding affinity to the mineralocorticoid receptor (MR) similar to aldosterone could play a role as a mineralocorticoid. This mineralocorticoid effect of cortisol is insignificant in normal situation because of 11 beta-hydroxysteroid dehydrogenase 2 (11β-HSD2) enzyme which converts cortisol to inactive cortisone. High levels of cortisol concentration may saturate 11β-HSD2 and mineralocorticoid effects appear (11). Moreover, a deficient 11β-HSD2 enzyme activity causes by mutations in the 11β-HSD2 gene results in cortisol saturation of MR. This excess stimulation of MR causes renal sodium retention, hypokalemia, and decreased of plasma renin and aldosterone secretion (12). In the light of these findings, a possible mutation or polymorphism in 11β-HSD2 gene may be the reason for differences in blood pressure levels and variations of serum potassium and sodium levels in patients with CS.

Another mechanism to explain hypokalemia and metabolic alkalosis in CD could be that direct ACTH contribution to the mineralocorticoid excess-like state of ADCS. ACTH can inhibit 11β-HSD2 both directly and/or triggering an inhibitory adrenal product (3). In consistence with these, it was suggested that increased levels of corticosterone and deoxycorticosterone, which controls mineralocorticoid activity, could be correlated with hypokalemia in CD (13, 14). Further investigations are needed to explain the role of 11β-HSD2 gene and its relation to biochemical and clinical findings in patients with CS.

CONCLUSION

In conclusion, this case highlighted the prominence of considering CD in the differential diagnosis of severe hypokalemia and metabolic alkalosis that could be a crucial part of biochemical features in CD. Large series are needed to assess the true incidence and severity of hypokalemia and metabolic alkalosis and to explain the mechanisms involved in CD.

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REFERENCES

1. Nishioka H, Yamada S. Cushing's Disease. Journal of clinical medicine. 2019;8(11).

2. Nieman LK. Cushing's syndrome: update on signs, symptoms and biochemical screening. European journal of endocrinology / European Federation of Endocrine Societies. 2015;173(4):M33-8.

3. Torpy DJ, Mullen N, Ilias I, Nieman LK. Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. Annals of the New York Academy of Sciences. 2002;970:134-44.

4. Martinez-Valles MA, Palafox-Cazarez A, Paredes-Avina JA. Severe hypokalemia, metabolic alkalosis and hypertension in a 54 year old male with ectopic ACTH syndrome: a case report. Cases journal. 2009;2:6174.

5. Badiu C, Capatana C, Cristofor D, Mircescu G, Coculescu M. APPARENT MINERALOCORTICOID EXCESS IN A CASE OF LUNG PARANEOPLASTIC CUSHING SYNDROME. Acta Endocrinologica (1841-0987). 2005;1(1).

6. Kishimoto S, Hirota K, Segawa H, Fukuda K. Ectopic ACTH syndrome revealed as severe hypokalemia and persistent hypertension during the perioperative period: a case report. Journal of anesthesia. 2011;25(1):104-7.

7. Kikuchi H, Yoshimoto T, Tanaka H, Tsujimoto K, Yamamura C, Arai Y, et al. Periodic hypokalemia associated with cyclic Cushing's syndrome. CEN case reports. 2014;3(1):80-5.

8. Kaltsas GA, Giannulis MG, Newell-Price JD, Dacie JE, Thakkar C, Afshar F, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. The Journal of clinical endocrinology and metabolism. 1999;84(2):487-92.

9. Pecori Giraldi F, Moro M, Cavagnini F, Study Group on the Hypothalamo-Pituitary-Adrenal Axis of the Italian Society of E. Gender-related differences in the presentation and course of Cushing's disease. The Journal of clinical endocrinology and metabolism. 2003;88(4):1554-8.

10. Titan SM, Gebara OC, Callas SH, Hoff AO, Hoff PM, Galvão P. Case report: a rare cause of metabolic alkalosis. Nephrology Dialysis Transplantation Plus. 2011;4(3):164-6.

11. Ulick S, Wang JZ, Blumenfeld JD, Pickering TG. Cortisol inactivation overload: a mechanism of mineralocorticoid hypertension in the ectopic adrenocorticotropin syndrome. The Journal of clinical endocrinology and metabolism. 1992;74(5):963-7.

12. Seckl JR. 11 beta-hydroxysteroid dehydrogenase isoforms and their implications for blood pressure regulation. European journal of clinical investigation. 1993;23(10):589-601.

13. Schambelan M, Slaton PE, Jr., Biglieri EG. Mineralocorticoid production in hyperadrenocorticism. Role in pathogenesis of hypokalemic alkalosis. The American journal of medicine. 1971;51(3):299-303.

14. Ferrari P, Krozowski Z. Role of the 11beta-hydroxysteroid dehydrogenase type 2 in blood pressure regulation. Kidney international. 2000;57(4):1374-81.