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Original Article

A Rare Cause of Hypokalemia: Ectopic ACTH Syndrome

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ABSTRACT

The most common cause of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome is a benign ACTH-producing pituitary tumour or, less frequently, ectopic ACTH production from non-pituitary tumours. Ectopic ACTH syndrome occurs more commonly in men and usually presents after 40 years. It is most commonly associated with small cell lung cancer. Although this syndrome is associated with severe hypercortisolemia, some findings of Cushing's syndrome, such as central obesity, may not be observed due to underlying malignant diseases. In these cases, rapid metabolic disruption, anorexia, myopathy, glucose intolerance, hypokalemic alkalosis, and hyperpigmentation accompany the patients' clinical condition. In the current case report, we aimed to emphasize that ectopic ACTH syndrome should be kept in mind in the differential diagnosis, especially in the presence of hypokalemia accompanying hypertension and proximal muscle weakness, if the patient also has progressive weight loss.

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Introduction

Cushing's syndrome (CS) is an endocrine disorder characterized by excessive cortisol production. Endogenous CS is a rare disease with an annual incidence of 0.7–2.4 per million. CS patients can show signs and symptoms such as moon face, trunkal obesity, hypertension, fatigue, amenorrhea, hirsutism, fragile skin that easily bruises striae, and osteoporosis.[1] The most common cause is iatrogenic CS due to long-term use of glucocorticoids. Endogenous CS occurs due to secretion of adrenocorticotropic (ACTH) and corticotropin-releasing hormone (CRH) from the pituitary and non-pituitary sources or excessive glucocorticoid secretion as a result of the adrenal gland's pathologies. The most common cause of ACTH-dependent CS is a benign ACTH-producing pituitary tumour (Cushing's disease; CH, 70-80%) or less frequently (15-20%) ectopic ACTH/CRH production from non-pituitary tumours.

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Ectopic ACTH secretion is a rare paraneoplastic syndrome associated with a large group of tumours, most of which are neuroendocrine cells.[2] Ectopic ACTH secretion is the first described paraneoplastic endocrine syndrome in the literature, and it accounts for only 10-20% of all ACTH-dependent CS cases.[3] It is most commonly associated with small cell carcinoma of the lung (SCLC).[4] Although this syndrome is associated with severe hypercortisolemia findings, some findings of CS, such as central obesity, may not be observed due to underlying malignant diseases. It should be considered in the differential diagnosis, especially if hypertension, proximal muscle weakness, hypokalemia and weight loss accompany. Herein we present a patient who developed ectopic ACTH syndrome due to SCLC.

Case Report

A 66-year-old male patient with a history of hypertension and coronary artery disease was admitted to our outpatient clinic with complaints of weakness, fatigue, proximal muscle weakness, hoarseness and weight loss for the last two weeks. There was no pathological finding in his physical examination, and he had a 40 pack/year smoking history. Laboratory tests revealed hypokalemia, metabolic alkalosis and hypercortisolemia (*Table 1*). The patient received oral and intravenous potassium replacement to correct hypokalemia. We performed a 1 mg dexamethasone suppression test (DST) due to high basal cortisol and ACTH levels. The cortisol level was 45 mcg/dL after DST. A pituitary magnetic resonance imaging

Table 1. Laboratory values of the patient at the time of admission.

Variables	Value (reference ranges)
Glucose (mg/dL)	107 (74-100)
Urea (mg/dL)	31 (19-49)
Creatinine (mg/dL)	0.66 (0.7-1.2)
AST (U/L)	35 (0-40)
ALT (U/L)	33 (0-41)
Sodium (mEq/L)	145 (136-145)
Potassium (mEq/L)	2.34 (3.5-5.1)
Corrected calcium (mg/dL)	8.4 (8.6-10.2)
Magnesium (mg/dL)	1.96 (1.6-2.69
pH	7.51 (7.35-7.45)
Bicarbonate (mmol/L)	34.7 (21-26)
Renin (ng/mL/h)	1.96 (0.98-4.18)
Aldosteron (ng/dL)	<5 (3-16)
ACTH (pg/mL)	311 (0-46)
Cortizol (µg/dL)	(6.2-19.4)
Basal	55
1 mg DST	45.3
8 mg DST	51

AST: alanine aminotransferase, ALT: aspartate aminotransferase, ACTH: adrenocorticotropic hormone, DST: dexamethasone suppression test.

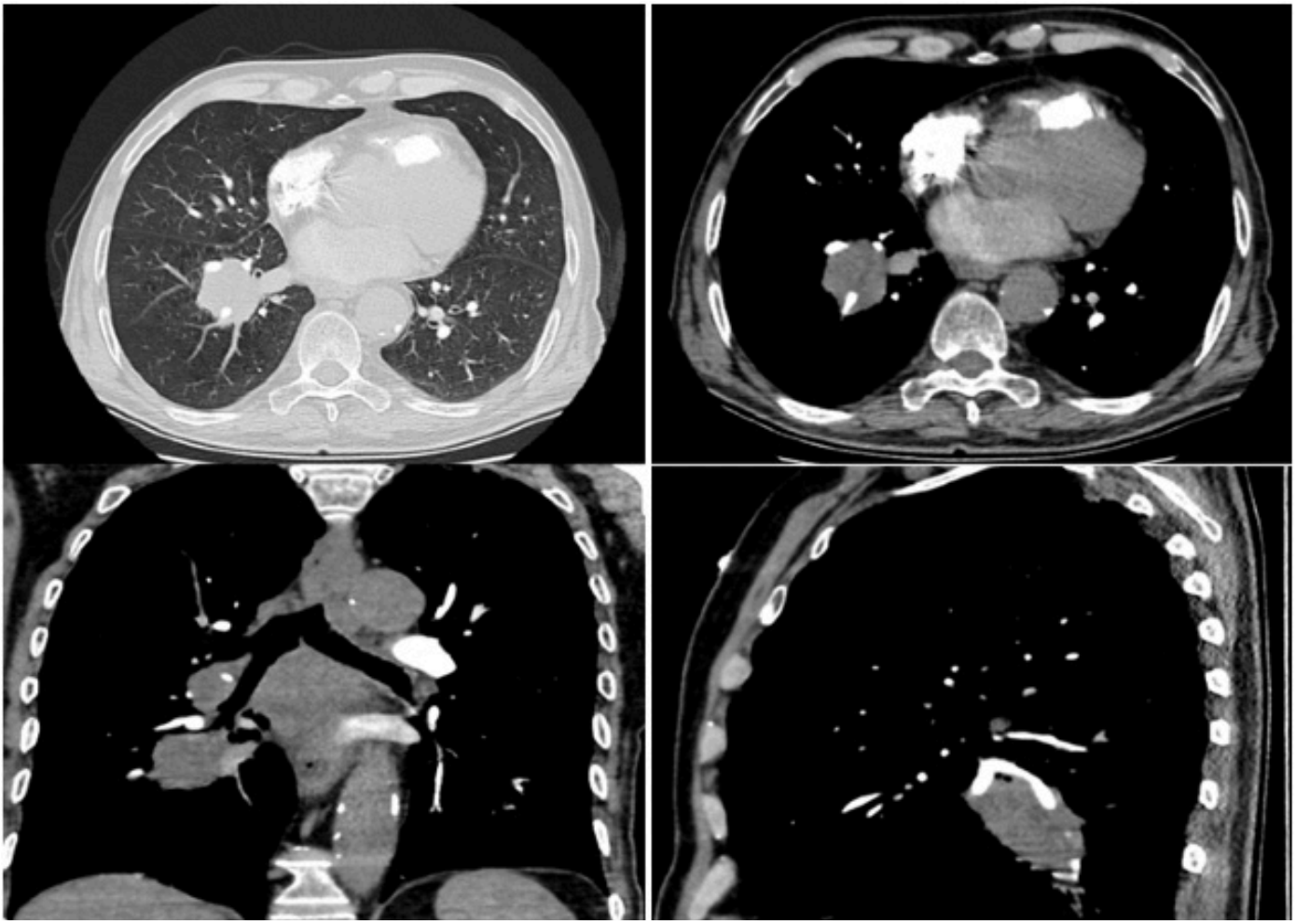

Table 1. Computed tomography images of the lesion in the lung.

(MRI) did not show adenoma in the pituitary region. There was no suppression of cortisol level in the high-dose DST test. On thoracic high-resolution computerised tomography (HRCT) imaging, a mass lesion measuring 4 cm and a soft tissue thickening of approximately 35 mm in the right hilar region was observed (*Picture 1*). The pathological examination of the biopsy taken from the mass was compatible with SCLC, and we referred the patient to the oncology policlinic for further assessment and treatment.

Discussion

Ectopic ACTH syndrome is a rare paraneoplastic syndrome caused by ACTH secreting tumour. SCLC and bronchopulmonary carcinoid tumours are the most common causes of ectopic ACTH release. Ectopic ACTH syndrome occurs most often in men, usually over 40 years. In addition to the typical symptoms of hypercortisolemia such as fatigue, proximal myopathy, and striae, findings related to high ACTH levels such as severe hypokalemia and hyperpigmentation may be observed.[5] Weight gain is not as prominent in ectopic ACTH syndrome as in CS patients because of the accompanying malignancy. Patients who developed ectopic ACTH syndrome related to malign tumours have more severe symptoms and faster disease progression due to higher serum ACTH and cortisol secretion. Resection of the tumour causing ectopic ACTH release is the optimal treatment method. However, chemotherapy treatment is at the forefront because SCLCs have a low resectability rate and respond well to systemic therapy.[6] In patients with ectopic CS, 1-year survival is reported as 84% and 5-year survival as 70%.[7] In this case, we emphasized that malignant causes lead to ectopic ACTH syndrome, and it should be considered in the differential diagnosis of patients with resistant hypokalemia.

Conclusions

When patients use oral contraceptives with flank pain and hematuria, one of the differential diagnoses should be acute renal vein thrombosis. The treatment can change depending on the patient's prognosis and clinic. Patients without acute kidney injury can generally follow up with anticoagulant therapy. Thrombolytic treatment and thrombectomy should be considered primarily in patients with the presence of acute kidney injury, transplanted kidneys, and bilateral RVT or unilateral patients with a high thrombus load.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MT; Study Design: MC; Supervision: SK; Materials: RO, MT; Data Collection and/or Processing: MT; Statistical Analysis and/or Data Interpretation: SK; Literature Review: MT; Manuscript Preparation: MC; Critical Review: SIA.

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