

Hypokalemia Due to Ectopic Adrenocorticotrophic Hormone

Adil Ghaffar, MD; Tripti Singh, MD

ABSTRACT

Hypokalemia is a common disorder in clinical practice. The underlying pathophysiology can be attributed to 3 main mechanisms: insufficient potassium intake, excessive urinary or gastrointestinal losses, and transcellular shift. Renal loss is the most common cause of hypokalemia. Renal loss of potassium can occur due to diuretics, mineralocorticoid excess or hypercortisolism (Cushing syndrome). Among patients with Cushing syndrome, ectopic adrenocorticotrophic hormone (ACTH) is the most frequent cause. We present a case of hypokalemia and hypertension due to ectopic ACTH production leading to Cushing syndrome.

INTRODUCTION

In adults, hypokalemia, metabolic alkalosis, and hypertension are commonly associated with mineralocorticoid excess—either primary or secondary hyperaldosteronism—but there are other less common causes as well. These include inherited disorders such as Liddle syndrome, congenital deficiency of 11 beta-hydroxysteroid dehydrogenase 2, certain medications, or ectopic adrenocorticotrophic hormone (ACTH) secretion from cancers—especially small cell lung cancer.

Small cell lung cancer can present with various paraneoplastic endocrine syndromes, such as hypercalcemia due to ectopic parathyroid hormone secretion and hyponatremia due to antidiuretic hormone excess.¹ In addition, ectopic ACTH secretion associated with small cell lung cancer can be one such manifestation that presents with hypokalemic metabolic alkalosis and

systemic hypertension. Fifteen percent of cases with ectopic ACTH secretion arise from the tumor or its metastasis.¹⁻³ Here we describe a case of recurrent small cell lung cancer presenting with ectopic ACTH secretion.

CASE PRESENTATION

A 64-year-old female was admitted to the hospital after presenting with complaints of feeling weak and lightheadedness. Her history included stage IIIB small cell lung cancer, which was treated with chemoradiation in May 2020 and was currently in remission, paroxysmal atrial fibrillation, obesity, hypertension, and chronic obstructive pulmonary disease.

On examination, the patient's temperature was 36.8°F, respiratory rate was 14 breaths per minute, blood pressure was 200/106 mm Hg, heart rate was 40 beats per minute, and oxygen saturation was 96% on room air. On admission, she was started on nifedipine infusion for blood pressure control, along with oral and intravenous potassium repletion. Nephrology was consulted for worsening hypertension and hypokalemia.

Upon evaluation by nephrology, the patient denied any recent nausea, vomiting, or watery diarrhea. She denied any diuretic, steroid, or herbal medication use. She did not have any stigmata of Cushing syndrome (hypercortisolism), such as moon facies, supraclavicular fat pad, or purplish abdominal wall striae. Lung examination showed no rales, and no lower extremity edema was elicited. Her previous labs showed serum potassium levels in the range of 4-4.5 mmol/L and bicarbonate levels 24-28 mmol/L. In the past, her blood pressure was well controlled on metoprolol alone.

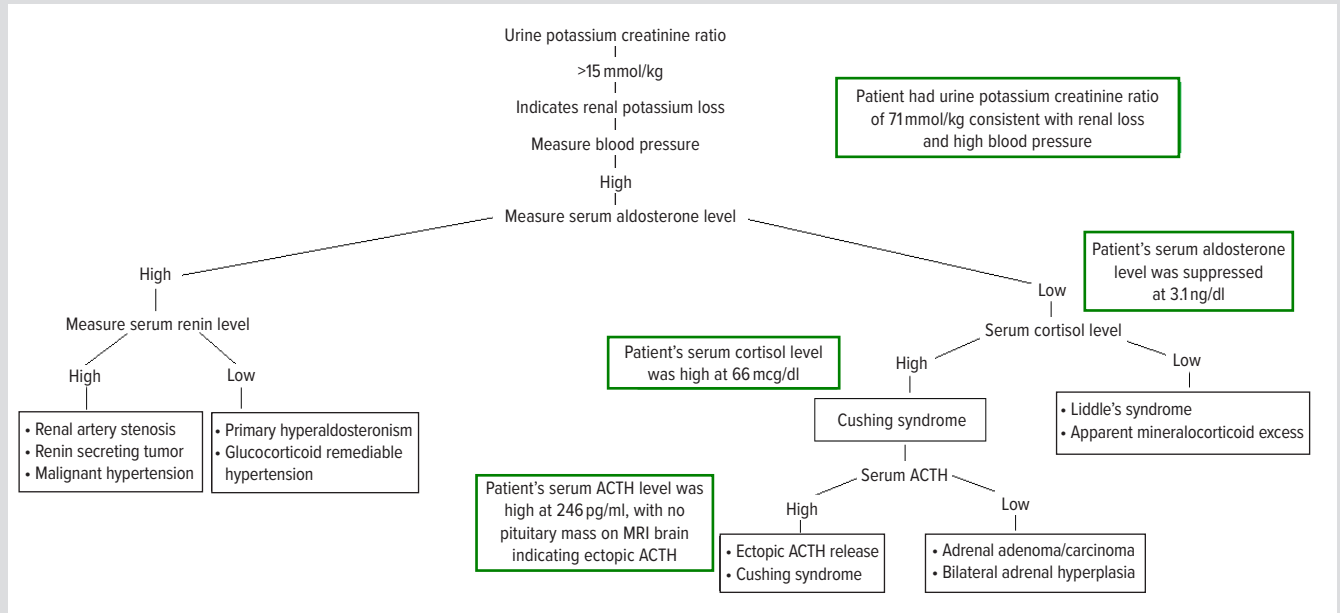
Computed tomography of the chest with intravenous contrast and a positron emission tomography (PET) scan showed enlarged left hilar lymph node with increased uptake suggestive of

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Author Affiliations: Saint Francis Medical Center, Cape Girardeau, Missouri (Ghaffar); Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (Singh).

Corresponding Author: Adil Ghaffar, MD, Saint Francis Medical Center, 211 Saint Francis Dr, Cape Girardeau, MO 63703; phone 573.331.3220; email aghaffar@sfmtc.net; ORCID ID 0000-0001-5989-1109

Figure 1. Algorithm for Work-up of Hypokalemia Due to Renal Potassium Wasting with Hypertension



Abbreviations: ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging.

recurrent small cell lung cancer, which was the source of ectopic ACTH. Magnetic resonance imaging of the brain did not show any pituitary masses. The patient was started on spironolactone. Serum potassium level and blood pressure normalized on a spironolactone dose of 200 mg daily. She was subsequently evaluated by the oncology team to restart chemotherapy for recurrent small cell lung cancer.

DISCUSSION

The cause of hypokalemia is usually obvious from the patient's history, but the urine potassium to creatinine ratio is an important test to differentiate between renal and extrarenal potassium wasting. If the ratio is more than 15 mmol/g, it signifies renal potassium wasting, which most commonly occurs with diuretic use. In the absence of diuretic use, differential diagnosis for new onset or worsening hypertension with hypokalemia and metabolic alkalosis includes hyperaldosteronism, Cushing syndrome, apparent mineralocorticoid excess (congenital deficiency of 11 beta-hydroxysteroid dehydrogenase 2 or drugs inhibiting it), or a genetic kidney tubular disorder such as Liddle syndrome (Figure 1).

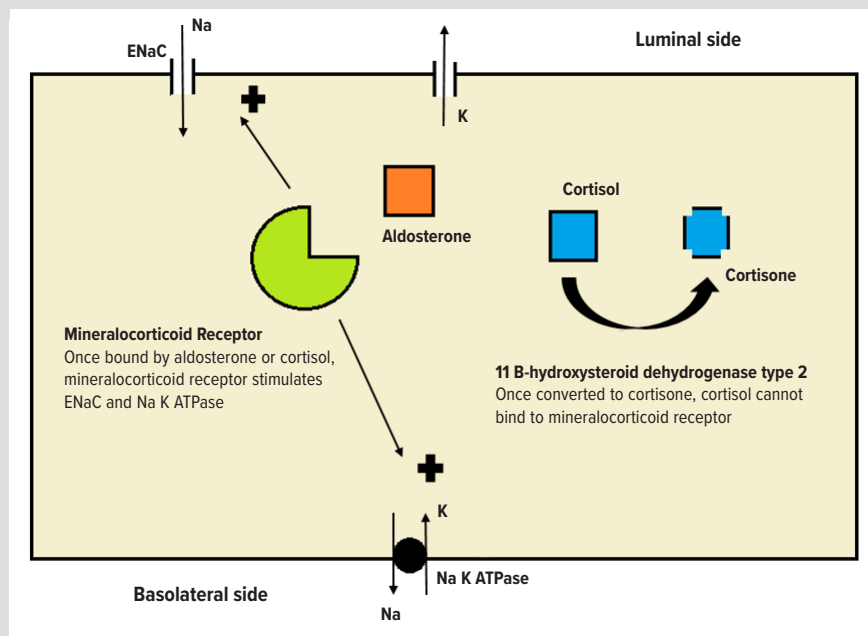
Our patient had an elevated urine potassium to creatinine ratio, indicating renal potassium wasting. She had no prior history of hypokalemia, which makes Liddle syndrome or apparent mineralocorticoid excess unlikely. She did not report any diuretic or licorice use (licorice can interfere with cortisol inactivation in the renal tubule). Due to worsening hypertension, hypokalemia, and metabolic alkalosis, the main differential was hyperaldosteronism, but both renin and aldosterone were suppressed. However, she had Cushing syndrome, which was responsible for

Table 1. Lab Results		
Blood Chemistry		
Potassium	2 mmol/L	Normal range: 3.5–5.0 mmol/L
Chloride	88 mmol/L	Normal range: 96–111 mmol/L
Bicarbonate	46 mmol/L	Normal range: 21–29 mmol/L
Magnesium	1.6 mg/dl	Normal range: 0.6–1.6 mg/dl
Creatinine	0.8 mg/dl	Normal range: 0.5–1.2 mg/dl
Urine Chemistry Results		
Urine potassium creatinine ratio	71 mmol/g	With hypokalemia, value >15 mmol/g signifies renal potassium wasting
Urine chloride	67 mmol/L	With hypochloremia, value >20 mmol/L indicates renal chloride wasting
Urine sodium	56 mmol/L	Varies, if <20 mmol/L indicates extra-renal volume depletion
Blood Hormonal Test Results		
Serum aldosterone	3.1 ng/dl	Upright: 4.0–31.0 ng/dL Supine: ≤16.0 ng/dL
Serum renin activity	0.4 ng/ml/hr	Supine: 0.2–1.6 ng/mL/hr Upright: 0.5–4.0 ng/mL/hr
Serum aldosterone renin ratio	0.78	Ratio >20 with aldosterone level >15 ng/dL suggests primary hyperaldosteronism
Serum cortisol	66 mcg/dl	AM: 3.7–19.4 mcg/dL PM: 2.9–17.3 mcg/dL
Serum ACTH	246 pg/ml	7.2–63.3 pg/ml
Abbreviation: ACTH, adrenocorticotropic hormone.		

her presentation.

Endogenous Cushing syndrome is rare and can be divided into corticotrophin-dependent (80%-85%) or corticotrophin independent (10%-15%) causes. It is estimated that 75% to 80% of cases are due to ACTH production from a pituitary adenoma, and 15% to 20% of cases are due to ectopic sources.^{6,7}

Figure 2. Principal Cell



Abbreviations: ENaC, epithelial sodium channel; K, potassium; Na, sodium; ROMK, renal outer medullary potassium channel.

In the principal cell of the collecting duct, aldosterone stimulates the epithelial sodium channel at the luminal membrane, driving lumen potential electronegative that stimulates potassium and hydrogen ion secretion in the lumen through the renal outer medullary potassium channel and hydrogen ATPase channel, respectively.

Cortisol also possesses mineralocorticoid activity and circulates in blood at a concentration 1000-fold greater than aldosterone. However, it does not act on the mineralocorticoid receptor in the principal cell due to its inactivation to cortisone by 11 beta-hydroxysteroid dehydrogenase type 2 (Figure 2).⁴ At very high levels of cortisol, however, 11 beta-hydroxysteroid dehydrogenase type 2 is not only overwhelmed but also inhibited by ACTH. This inhibition by ACTH is far more important, as it is rare to have hypokalemia and metabolic alkalosis in other causes of Cushing syndrome.⁵

Management of ectopic ACTH syndrome depends on treating the underlying malignancy. Until treatment of malignancy, spironolactone (mineralocorticoid receptor antagonist), amiloride (epithelial sodium channel blocker), and ketoconazole (inhibits steroid synthesis) can help improve hypertension and electrolyte imbalance.

Our patient did not have any peripheral stigmata of Cushing syndrome; however, her presentation was due to elevated cortisol from ectopic ACTH. It is unusual for the ectopic ACTH to present with classical clinical signs of Cushing's syndrome as there is exposure to high levels of glucocorticoids within a short period.

CONCLUSIONS

We recommend evaluation of serum cortisol level as part of the workup of new onset or worsening hypertension with hypokalemia and metabolic alkalosis, along with serum renin and aldosterone. Such an evaluation is critical, especially in a patient with known small cell lung cancer who presents with this triad.

Funding/Support: None declared.

Financial Disclosures: None declared.

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