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A paraneoplastic potassium and acid-base disturbance

NOTE: The scenario presented here is partly based on cases reported elsewhere by Martínez-Valles et al¹ and Fernández-Rodríguez et al.²

A 55-YEAR-OLD MAN is admitted to the hospital with generalized malaise, paresthesias, and severe hypertension. He says he had experienced agitation along with weakness on exertion 24 hours before presentation to the emergency department, with subsequent onset of paresthesias in his lower extremities and perioral area.

He is already known to have mild chronic obstructive pulmonary disease, with a ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) of less than 70% and an FEV₁ 85% of predicted. In addition, he was recently diagnosed with diabetes, resistant hypertension requiring maximum doses of 3 agents (a calcium channel blocker, an angiotensin-converting enzyme inhibitor, and a loop diuretic), and hyperlipidemia.

He is a current smoker with a 30-pack-year smoking history. He does not use alcohol. His family history is noncontributory.

His blood pressure is 190/110 mm Hg despite adherence to his 3-drug regimen. His oxygen saturation is 94% on room air, respiratory rate in the low 30s, and pulse 110 beats/minute. He has normal breath sounds, normal S1 and S2 with an S4 gallop, bilateral lower-extremity edema, truncal obesity, and abdominal striae. Electrocardiography shows tachycardia with first-degree atrioventricular block. Chest radiography shows an opacity in the right middle lung field. Initial laboratory results and those from 1 year ago are shown in Table 1.

ASSESSING ACID-BASE DISORDERS

1 What type of acid-base disorder does this patient have?

- ☐ Metabolic acidosis
- ☐ Respiratory acidosis
- ☐ Metabolic alkalosis
- ☐ Respiratory alkalosis

The patient has metabolic alkalosis.

A 5-step approach

If a patient has an acid-base disorder, one should use a 5-step process to characterize it (Table 2).³

1. **Acidosis or alkalosis?** The patient's arterial pH is 7.5, which is alkalemic because it is higher than 7.44.

2. **Metabolic or respiratory?** The primary process in our patient is overwhelmingly metabolic, as his partial pressure of carbon dioxide (Pco₂) is slightly elevated, a direction that would cause acidosis, not alkalosis.

3. **The anion gap** (the serum sodium concentration minus the sum of the chloride and bicarbonate concentrations) is normal at 8 mmol/L (DRG:HYBRiD-XL Immunoassay and Clinical Chemistry Analyzer, reference range 8–16).

4. **Is the disturbance compensated?** We have determined that this patient has a metabolic alkalemia; the question now is whether there is any compensation for the primary disturbance.

In metabolic alkalosis, the Pco₂ may increase by approximately 0.6 mm Hg (range 0.5–0.8) above the nominal normal level of 40 mm Hg for each 1-mmol/L increase in bicarbonate above the nominal normal level of 25 mmol/L.⁴ If the patient requires oxygen,

A 55-year-old smoker with COPD presents with malaise, paresthesias, and severe hypertension: What is the cause?

TABLE 1

Laboratory results on presentation and 1 year earlier

Test	Current level ^a	1 year earlier	Reference range
Sodium (mmol/L)	144	135	136–144
Potassium (mmol/L)	2.8	4.0	3.7–5.1
Chloride (mmol/L)	96	100	97–105
Bicarbonate (mmol/L)	40	28	22–30 ^b
Serum creatinine (mg/dL)	1.2	1.2	0.58–0.96
Blood urea nitrogen (mg/dL)	28	19	7–21
Glucose (mg/dL)	197		74–99
Calcium and magnesium	Normal		
Arterial blood gases			
pH	7.50	7.34	7.35–7.45
Pco ₂ (mm Hg)	51	40	34–46 ^c
Pao ₂ (mm Hg)	75	76	85–95
Bicarbonate (mmol/L)	40		22–26

^aAbnormal results are shown in bold.^bFor acid-base problem-solving, a value of 25 mmol/L is considered normal.^cFor acid-base problem-solving, a value of 40 mm Hg is considered normal.

An algorithmic approach can arrive at the cause of hypokalemic metabolic alkalosis with hypertension

the calculation may be unreliable, however, as hypoxemia may have an overriding influence on respiratory drive.

Patients with chronically high Pco₂ levels such as those with chronic obstructive pulmonary disease can become accustomed to high carbon dioxide levels and lose their hypercapnic respiratory drive. Giving oxygen supplementation is thought to decrease respiratory drive in these patients, so that they will breathe slower and retain more carbon dioxide. There is some degree of respiratory compensation for metabolic alkalosis that occurs by breathing less, though it is limited overall—even in very alkalotic patients, breathing less results in CO₂ retention, which, by displacing O₂ molecules in the alveoli, will in turn result in hypoxia. The brain then senses the hypoxia and makes one breathe faster, thereby limiting this compensation.

This patient's serum bicarbonate level is 40 mmol/L, or 15 mmol/L higher than the nominal normal level. If he is compensating, his Pco₂ should be $40 + (15 \times 0.6) = 49$

mm Hg, and in fact it is 51 mm Hg, which is within the normal range of expected compensation (47.5–52 mm Hg). Therefore, yes, he is compensating for the primary disturbance.

5. In metabolic acidosis, is there a delta gap? As our patient has metabolic alkalosis, not acidosis, this question does not apply in this case.

WHICH TEST TO FIND THE CAUSE?

2 Which is the best test to order next to determine the cause of this patient's hypokalemic metabolic alkalosis?

- ☐ Serum magnesium level
- ☐ Spot urine chloride
- ☐ Renal ultrasonography
- ☐ 24-hour urine collection for sodium, potassium, and chloride

The first step in the algorithm for hypokalemic metabolic alkalosis (**Figure 1**) is to obtain a spot urine chloride measurement. If this value is low, the hypokalemic metabolic alkalosis is volume-responsive; if it is high, the disturbance is volume-independent.

The patient's loop diuretic is withheld for 12 hours and a spot urine chloride is obtained, which is reported as 44 mmol/L. This high value suggests that a volume-independent hypokalemic metabolic alkalosis is present with potassium depletion.

As for the other answer choices:

Serum magnesium. Though hypomagnesemia can cause hypokalemia due to lack of inhibition of renal outer medullary potassium channels and subsequent increased excretion of potassium in the apical tubular membrane, it is not independently associated with acid-base disturbances.⁵

Renal ultrasonography gives information about structural kidney disease but is of limited utility in identifying the cause of hypokalemic metabolic alkalosis.

A 24-hour urine collection is unnecessary in this setting and would ultimately result in delay in diagnosis, as spot urine chloride is a more efficient means of rapidly distinguishing volume-responsive vs volume-independent causes of hypokalemic metabolic alkalosis.⁶

TABLE 2

'Rules of 5' for acid-base problem-solving**1 Determine the arterial pH**pH < 7.38 is acidemic, pH > 7.42 is alkalemic^a

Normal pH does not rule out an acid-base disorder

2 If the arterial pH is abnormal, determine whether the primary process is respiratory, metabolic, or both

	pH	Pco ₂	HCO ₃
Respiratory acidosis ^a	Low	High	—
Metabolic acidosis	Low	—	Low
Mixed respiratory and metabolic acidosis	Low	High	Low
Respiratory alkalosis	High	Low	—
Metabolic alkalosis	High	Varies ^b	High
Mixed respiratory and metabolic alkalosis	High	Low	High

3 Calculate the anion gap**Anion gap = sodium – (chloride + bicarbonate)**

If serum albumin is low, add 2.5 mmol/L to the anion gap for every 1 g the serum albumin is below normal

4 Check the degree of compensation (respiratory or metabolic)PCO₂ and bicarbonate should increase or decrease togetherNormal levels: bicarbonate 25 mmol/L, PCO₂ 40 mm Hg**Acute respiratory acidosis:** For every 10-mm Hg increase in PCO₂, bicarbonate should increase by 1 mmol/L**Chronic respiratory acidosis (> 48 hours):** For every 10-mm Hg increase in PCO₂, bicarbonate should increase by 4 mmol/L**Metabolic acidosis:** For every 1-mmol/L decrease in bicarbonate, PCO₂ should decrease by 1.3 mm Hg**Acute respiratory alkalosis:** For every 10-mm Hg decrease in PCO₂, bicarbonate should decrease by 2 mmol/L**Chronic respiratory alkalosis (> 48 hours):** For every 10-mm Hg decrease in PCO₂, bicarbonate should decrease by 5 mmol/L**Metabolic alkalosis:** For every 1-mmol/L increase in bicarbonate, PCO₂ may increase by 0.6 mm Hg**5 If the patient has metabolic acidosis with an elevated anion gap, assess for 'delta gap' (whether the decrease in bicarbonate = the increase in anion gap)****Delta gap = change in anion gap / change in bicarbonate**
([anion gap – 10] / [24 – bicarbonate])

> 1: Additional metabolic alkalosis

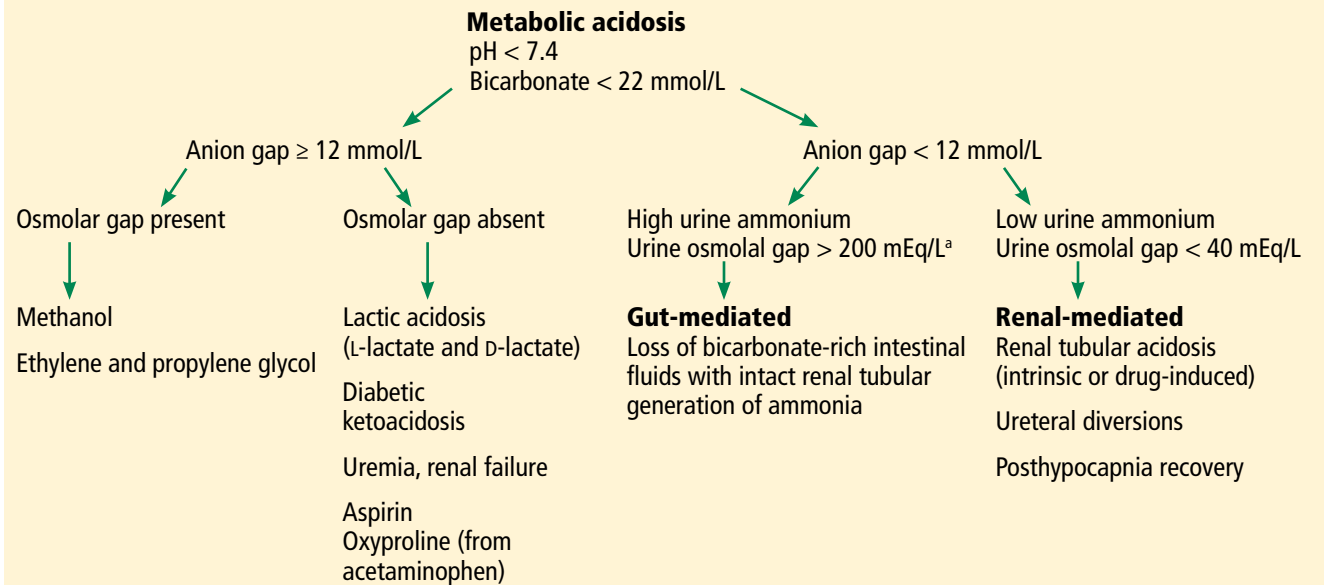
1: No additional disturbance present

< 1: Additional non-anion gap metabolic acidosis present

^a Acidosis and alkalosis refer to acid-base disturbances with determined metabolic or respiratory etiologies. Alkalemia and acidemia refer to disturbances in blood pH prior to determination of the underlying metabolic/respiratory cause.^b PCO₂ in metabolic alkalosis may vary depending on the clinical context, as compensation for metabolic alkalosis requires decreased respiratory drive, which may be influenced by other factors (ie, hypoxia).PCO₂ = partial pressure of carbon dioxide

Adapted from Mani S, Rutecki GW. A patient with altered mental status and an acid-base disturbance. Cleve Clin J Med 2017; 84(1):27–34. Copyright © 2017 The Cleveland Clinic Foundation. All rights reserved.

HYPOKALEMIA AND METABOLIC ALKALOSIS



^a Urine osmolal gap = measured urine osmolality minus the calculated urine osmolality, where calculated urine osmolality = $2[\text{Na}^+] + 2[\text{K}^+] + (\text{urine urea nitrogen [mg/dL]} / 2.8) + (\text{urine glucose [mg/dL]} / 18)$.²⁷

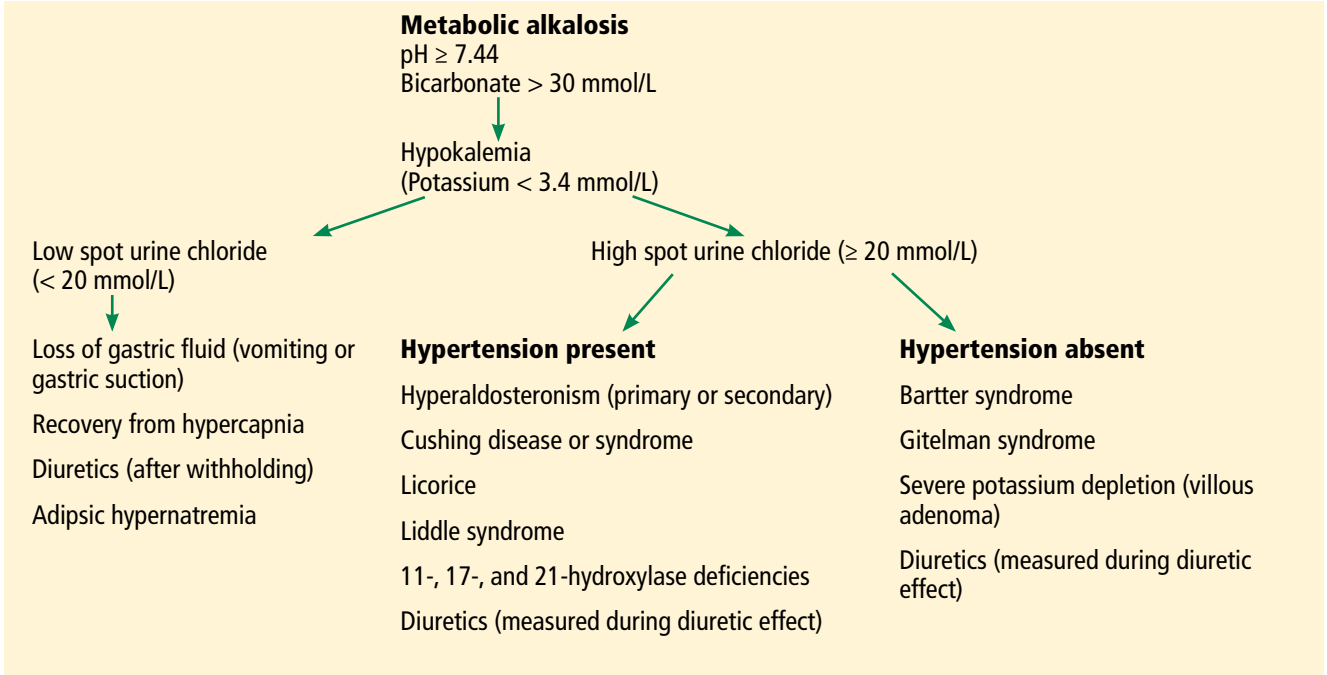


Figure 1. Algorithms for determining causes of metabolic acid-base disturbances.

■ IS HIS HYPERTENSION SECONDARY? IF SO, WHAT IS THE CAUSE?

Several features of this case suggest that the patient's hypertension is secondary rather

than primary. It is of recent onset. The patient's family history is noncontributory, and his hypertension is resistant to the use of maximum doses of 3 antihypertensive agents.

TABLE 3

Renin and aldosterone values in hypokalemic metabolic alkalosis with high urine chloride

Renin and aldosterone	Elevated blood pressure	Normotensive
High renin, high aldosterone, normal ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA)	Renal artery stenosis	Bartter syndrome
	Renin-secreting tumor	Gitelman syndrome
	Diuretics	Severe potassium depletion (villous adenoma)
		Diuretics
Low renin, high aldosterone, high PAC–PRA ratio	Primary hyperaldosteronism	
Low renin, low aldosterone, normal PAC–PRA ratio	Licorice	
	Cushing disease or syndrome	
	Hydroxylase deficiencies	
	Liddle syndrome	

3 Which of the following causes of secondary hypertension is not commonly associated with hypokalemia and metabolic alkalosis?

- ☐ Hyperaldosteronism
- ☐ Liddle syndrome
- ☐ Cushing syndrome
- ☐ Renal parenchymal disease
- ☐ Chronic licorice ingestion

Renal parenchymal disease is a cause of resistant hypertension, but it is not characterized by metabolic alkalosis, hypokalemia, and elevated urine chloride,⁷ while the others listed here—hyperaldosteronism, Liddle syndrome, Cushing syndrome, and chronic licorice ingestion—are. Other common causes of resistant hypertension without these metabolic abnormalities include obstructive sleep apnea, alcohol abuse, and nonadherence to treatment.

While treatment of hypertension with loop diuretics can result in hypokalemia and metabolic alkalosis due to the effect of these drugs on potassium reabsorption in the loop of Henle, the patient's hypokalemia persisted after this agent was withdrawn.⁸

Causes of hypokalemic metabolic alkalosis with and without hypertension are further delineated in **Figure 1**.

Additional diagnostic testing:**Plasma renin and plasma aldosterone**

At this juncture, the differential diagnosis for this patient's potassium depletion, metabolic alkalosis, high urine chloride, and hypertension has been narrowed to primary or secondary hyperaldosteronism, surreptitious mineralocorticoid ingestion, Cushing syndrome, licorice ingestion, Liddle syndrome, or one of the 3 hydroxylase deficiencies (11-, 17-, and 21-) (**Figure 1**).

Although clues in the history, physical examination, and imaging may suggest a specific cause of his abnormal laboratory values, the next step in the diagnostic workup is to measure the plasma renin and aldosterone levels (**Table 3**).

■ HYPERALDOSTERONISM

4 Hyperaldosteronism is associated with which of the following patterns of renin and aldosterone values?

- ☐ High renin, high aldosterone, normal ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA)
- ☐ Low renin, low aldosterone, normal PAC–PRA ratio

Several features suggest that his hypertension is secondary rather than primary

- ☐ Low renin, high aldosterone, high PAC–PRA ratio
- ☐ High renin, low aldosterone, low PAC–PRA ratio

The pattern of low renin, high aldosterone, and high PAC–PRA ratio is associated with hyperaldosteronism.

Primary hyperaldosteronism

Primary hyperaldosteronism is one of the most common causes of resistant hypertension and is underappreciated, being diagnosed in up to 20% of patients referred to hypertension specialty clinics.⁷ Potassium levels may be normal, likely contributing to its lack of recognition in this target population.

Primary hyperaldosteronism should be suspected in patients who have a plasma aldosterone PAC–PRA ratio greater than 20 with elevated plasma aldosterone concentrations (> 15 ng/dL).

Persistently elevated aldosterone levels in the setting of elevated plasma volume is proof that aldosterone secretion is independent of the renin-angiotensin-aldosterone axis, and therefore is autonomous (secondary to adrenal tumor or hyperplasia). Further testing in the form of oral salt loading, saline infusion, or fludrocortisone (a sodium-retaining steroid) administration is thus required to confirm inappropriate, autonomous aldosterone secretion.⁹

After establishing the diagnosis of primary hyperaldosteronism, one should determine the subtype (ie, due to an adrenal carcinoma, unilateral hypersecreting adenoma, or unilateral or bilateral hyperplasia). Further testing includes adrenal computed tomography (CT) to rule out adrenal carcinomas, which are suspected with adenomas larger than 4 cm. Though part of the diagnostic workup, CT as a means of confirmational testing alone does not preclude the possibility of bilateral adrenal hyperplasia in some patients, even in the presence of an adrenal adenoma. For this reason, adrenal venous sampling is required to definitively determine whether the condition is due to a hypersecreting adrenal adenoma or unilateral or bilateral hyperplasia.^{9,10}

Treatment of primary hyperaldosteronism depends on the subtype of the disease and involves salt restriction in addition to an aldosterone antagonist (spironolactone or eplerenone in the case of bilateral disease) or surgery (unilateral disease).^{9,11,12}

sterone antagonist (spironolactone or eplerenone in the case of bilateral disease) or surgery (unilateral disease).^{9,11,12}

Secondary hyperaldosteronism

Secondary hyperaldosteronism should be suspected when plasma renin and aldosterone levels are both elevated with a PAC–PRA ratio less than 10.

This pattern is most commonly seen with diuretic use but can also be a consequence of renal artery stenosis or, rarely, a renin-secreting tumor.¹³ Renal artery stenosis is a common finding in patients with hypertension undergoing cardiac catheterization, which is not surprising as more than 90% of such stenoses are atherosclerotic.⁷ Renin-secreting tumors are exceedingly rare, with fewer than 100 cases reported in the literature, and are more common in younger individuals.¹³

Our patient has low-normal aldosterone and plasma renin

On further testing, this patient's plasma aldosterone level is 2.55 ng/dL (normal < 15 ng/dL), his plasma renin activity is 0.53 ng/mL/hour (normal 0.2–2.8 ng/mL/hour), and his PAC–PRA ratio is therefore 4.81.

The categories discussed thus far have included primary and secondary hyperaldosteronism, which typically do not present with low to normal levels of both renin and aldosterone. Surreptitious mineralocorticoid use could present in this manner, but is unlikely in this patient, whose medications do not include fludrocortisone.

The low-normal values thus lead to consideration of a third category: apparent mineralocorticoid excess. Diseases in this category such as Cushing disease or adrenocorticotrophic hormone (ACTH) excess are characterized by increases in corticosteroids so that the potassium depletion, metabolic alkalosis, and hypertension are not a consequence of renin and aldosterone but rather the excess corticosteroids.¹⁴

Causes of apparent mineralocorticoid excess

There are several possible causes of mineralocorticoid excess associated with hypertension and hypokalemic metabolic alkalosis not due to renin and aldosterone.

Primary hyperaldosteronism is one of the most common causes of resistant hypertension and is underappreciated

Chronic licorice ingestion in high volumes is one such cause and is thought to result in inhibition of 11 β -hydroxysteroid dehydrogenase or possibly cortisol oxidase by licorice's active component, glycyrrhetic acid. This inhibition results in an inability to convert cortisol to cortisone. The cortisol excess binds to mineralocorticoid receptors, and acting like aldosterone, results in hypertension and hypokalemic metabolic alkalosis as well as feedback inhibition of renin and aldosterone levels.¹⁵

Partial hydroxylase deficiencies, though rare, should also be considered as a cause of hypokalemic metabolic alkalosis, hypertension, and, potentially, hirsutism and clitoromegaly in women. They can be diagnosed with elevated levels of 17-ketosteroids and dehydroepiandrosterone sulfate, both of which, in excess, may act on aldosterone receptors in a manner similar to cortisol.¹⁶

Liddle syndrome, a rare autosomal dominant condition, may also present with suppressed levels of both renin and aldosterone. In contrast to the disorders of nonaldosterone mineralocorticoid excess, however, the sodium channel defect in Liddle syndrome is characterized by a primary increase in sodium reabsorption in the collecting tubule and potassium wasting. The resultant volume expansion leads to suppressed renin and aldosterone levels and hypertension with low potassium and elevated bicarbonate concentrations.¹⁷

Liddle syndrome is commonly diagnosed in childhood but may go unrecognized due to occasional absence of hypokalemia at presentation. Potassium-sparing diuretics such as amiloride or triamterene are the mainstays of treatment.¹⁸

Hypercortisolism results in hypokalemic metabolic alkalosis through the effect of excess cortisol on mineralocorticoid receptors, similar to what occurs in chronic licorice ingestion. Under normal conditions, 11 β -hydroxysteroid dehydrogenase converts cortisol to cortisone and is the rate-limiting step in the mineralocorticoid action of cortisol. When plasma cortisol levels are in excess, however, the enzyme is saturated so that its action is insufficient, resulting in cortisol binding to mineralocorticoid receptors to

TABLE 4

Effects of hypercortisolism

Organ system	Manifestation
Cardiovascular	Hypertension, thromboembolism, cardiomyopathy
Metabolic	Glucose intolerance/diabetes, hyperlipidemia, obesity
Reproductive	Menstrual irregularities, hirsutism, changes in libido, virilization
Dermatologic	Easy bruisability, striae, skin atrophy, hyperpigmentation, oily skin
Musculoskeletal	Proximal muscle wasting, osteopenia/osteoporosis
Neuropsychiatric	Psychosis, emotional lability, depression, anxiety, sleep apnea
Immunologic function	Increased susceptibility to fungal and bacterial infection, opportunistic infections
Ophthalmologic	Glaucoma, cataracts, central serous chorioretinopathy, hypertensive retinopathy

produce effects similar to that of aldosterone on acid-base and electrolyte balance and blood pressure.¹⁹

The increase in blood pressure that is associated with elevated plasma levels of cortisol is not attributable solely to its effect on mineralocorticoid receptors, however. The pathogenesis is multifactorial and not fully understood, but it also is thought to involve increased peripheral vascular sensitivity to adrenergic agonists, increased hepatic production of angiotensinogen, as well as direct and indirect cardiotoxic effects via metabolic and electrolyte aberrations.²⁰ Other common effects and manifestations of hypercortisolism are listed in Table 4.

Rates of cardiovascular and all-cause mortality are increased in patients with long-term hypercortisolism, even after plasma concentrations of cortisol are normalized.²¹

Figure 2 shows the cascade of the hypothalamic-pituitary-adrenal axis.

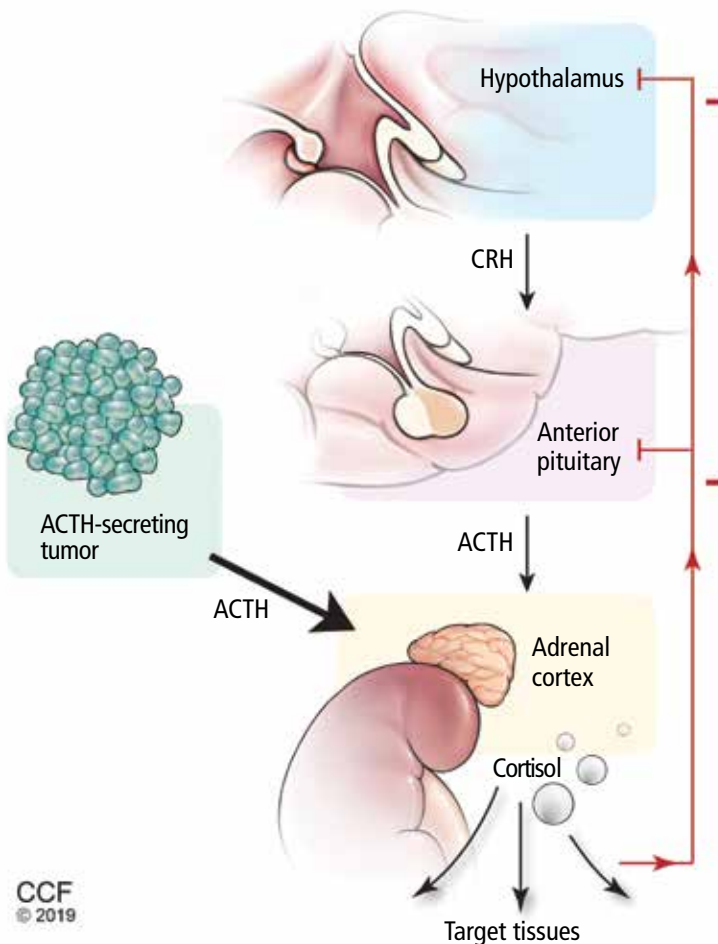


Figure 2. The hypothalamic-pituitary-adrenal axis.

CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone

■ TESTING FOR HYPERCORTISOLISM IN OUR PATIENT

Given the patient's clinical presentation and laboratory and imaging findings with normal plasma renin and aldosterone levels, a workup for suspected hypercortisolism is initiated.

Initial diagnostic testing for hypercortisolism depends on the degree of clinical suspicion. In those with low probability of the disease, testing should consist of 1 of the following, as a single negative test may be sufficient to rule out the disease:

- 24-hour urinary cortisol levels
 - Overnight dexamethasone suppression testing
 - Late-night salivary cortisol measurements.
- In those with a high index of suspicion,

2 of the aforementioned tests should be performed, as 1 normal result may not be sufficient to exclude the diagnosis.^{22,23}

A 24-hour urinary cortisol collection and overnight dexamethasone suppression test are obtained. His 24-hour urinary free cortisol level is elevated at 6,600 μg (normal 4–100), and suppression testing with 8 mg of dexamethasone (a form of “high-dose” testing) demonstrates only an 8% decline in serum cortisol levels. Cortisol should generally drop more than 90%.

Morning serum cortisol concentration is less than 5 $\mu\text{g/dL}$ (140 nmol/L) in most patients with Cushing disease (ie, a pituitary tumor), and is usually undetectable in normal subjects. Only about 50% of neuroendocrine ACTH-secreting tumors will suppress with this test.

The patient's clinical presentation, in conjunction with his diagnostic testing, are thus consistent with Cushing syndrome.

■ CUSHING SYNDROME

Cushing syndrome is most often exogenous or iatrogenic, ie, a result of supraphysiologic doses of glucocorticoids used to treat a variety of inflammatory, autoimmune, and neoplastic conditions.

Endogenous Cushing syndrome, on the other hand, is rare, with an estimated prevalence of 0.7 to 2.4 cases per million per year. ACTH-dependent causes account for 80% of endogenous Cushing syndrome cases, with ACTH-secreting pituitary adenomas (Cushing disease) accounting for 75% to 80% and ectopic ACTH secretion accounting for 15% to 20%. Less than 1% of cases are due to tumors that produce corticotropin-releasing hormone (CRH).

ACTH-independent Cushing syndrome is diagnosed in 20% of endogenous cases and is most commonly caused by a unilateral adrenal tumor. Rare causes of ACTH-independent disease include adrenal carcinoma, McCune-Albright syndrome, and adrenal hyperplasia.²⁴

The patient's ACTH is high

To determine whether this is an ACTH-dependent or independent process, the next step is to order an ACTH level. His ACTH level is



Figure 3. Computed tomography of the chest depicting biopsy-proven small-cell carcinoma (arrows).

high at 107 pg/mL (normal < 46 pg/mL), confirming the diagnosis of ACTH-dependent Cushing syndrome.

To find out if this ACTH-dependent process is due to a pituitary adenoma, magnetic resonance imaging (MRI) of the pituitary is obtained but is normal.

Large masses (> 6 mm) strongly suggest Cushing disease, but these tumors are often small and may be missed even with more advanced imaging techniques. Corticotropin-secreting adenomas arising from normal cells in the pituitary retain some sensitivity to glucocorticoid negative feedback and CRH stimulation, and thus high-dose dexamethasone suppression testing in conjunction with CRH stimulation testing can be used to differentiate Cushing disease from ectopic ACTH secretion.^{24,25} Both of these tests have poor diagnostic accuracy, however, and thus inferior petrosal sampling remains the gold standard for the diagnosis of Cushing disease.

Given this patient's history of smoking and a right hilar pulmonary opacity on chest radiography, inferior petrosal sampling was deferred in favor of CT of the chest, which showed a right consolidative lung lesion (**Figure 3**). Subsequent CT-guided fine-needle biopsy demonstrated a small-cell carcinoma.

■ ACTH-SECRETING TUMORS

5 Cushing syndrome due to ectopic ACTH secretion is most commonly attributed to which of the following tumors?

- ☐ Small-cell lung carcinoma
- ☐ Pancreatic carcinoma
- ☐ Medullary thyroid carcinoma
- ☐ Gastrinoma

Severe cases of Cushing syndrome are often attributable to ectopic ACTH secretion due to an underlying malignancy, most commonly small-cell lung carcinoma or neuroendocrine tumors of pulmonary origin. Other causes include pancreatic and thymic neuroendocrine tumors, gastrinomas, and medullary thyroid carcinoma.^{25,26}

Because most ACTH-producing tumors are intrathoracic, initial imaging in cases of suspected ectopic ACTH secretion should focus on the chest, with CT the usual first choice. Octreotide scintigraphy can also be useful in localizing disease, as many neuroendocrine tumors express somatostatin receptors. Specialized positron-emission tomography scans may also be helpful in tumor identification.²⁴

Severe cases of Cushing syndrome are often attributable to ectopic ACTH secretion

TREATMENT OF CUSHING SYNDROME DUE TO ECTOPIC ACTH SECRETION

6 Which of the following is most appropriate medical therapy for suppression of cortisol secretion in Cushing syndrome due to ectopic ACTH secretion?

- ☐ Spironolactone
- ☐ Dexamethasone
- ☐ Somatostatin
- ☐ Estrogen
- ☐ Ketoconazole

Hyperglycemia, hypokalemia, hypertension, psychiatric disturbances, venous thromboembolism, and systemic infections appear to be common in ectopic ACTH syndrome and often correlate with the degree of hypercortisolemia. Severe Cushing syndrome due to ectopic ACTH secretion is an emergency requiring prompt control of cortisol secretion.

First-line treatments include steroidogenesis inhibitors (ketoconazole, metyrapone, etomidate, mitotane) and glucocorticoid receptor antagonists (mifepristone). High-dose spironolactone and eplerenone can also be used to treat the hypertension and hypokalemia associated with mineralocorticoid receptor stimulation. Definitive treatment involves surgical resection, chemotherapy, or radiotherapy when applicable.^{24,25}

After confirmation of the diagnosis, the patient is prescribed ketoconazole and spironolactone, with substantial improvement. He subsequently is started on combination chemotherapy and radiation therapy for his small-cell lung carcinoma.

DISCUSSION

The differential diagnosis for hypokalemia is broad and relies on information obtained during the history and physical examination, followed by interpretation of selected laboratory results. Myriad pathologies in diverse organ systems, eg, diarrhea, renal tubular acidosis, and adrenal disease, may be responsible for a low serum potassium. Further categorizing potassium depletion on the basis of an associated acid-base disturbance, such as metabolic alkalosis, allows one to use an algorithmic approach that can identify specific etiologies responsible for both the potassium and the acid-base disturbances.

Using the spot urine chloride in the setting of hypokalemic metabolic alkalosis with or without hypertension can narrow the differential diagnosis and allow additional clinical findings to guide clinical problem-solving and decision-making, even for conditions not commonly encountered in routine medical practice.

Obtaining renin and aldosterone measurements in patients with potassium depletion, metabolic alkalosis, high urine chloride excretion, and hypertension permits further categorization into 3 clinical groups: elevated aldosterone and renin (secondary hyperaldosteronism), elevated aldosterone and low renin (primary hyperaldosteronism), or apparent mineralocorticoid excess wherein neither renin nor aldosterone are responsible for the syndrome.

The patient in our case had apparent mineralocorticoid excess as a consequence of an ACTH-producing small-cell carcinoma. ■

REFERENCES

- Martínez-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 J* 2009; 2:6174. doi:10.4076/1757-1626-2-6174
- Fernández-Rodríguez E, Villar-Taibo R, Pinal-Orsorio I, et al. Severe hypertension and hypokalemia as first clinical manifestations in ectopic Cushing's syndrome. *Arq Bras Endocrinol Metabol* 2008; 52(6):1066–1070. PMID:18820819
- Mani S, Rutecki GW. A patient with altered mental status and an acid-base disturbance. *Cleve Clin J Med* 2017; 84(1):27–34. doi:10.3949/ccjm.84a.16042
- Adrogue HJ, Madias NE. Secondary responses to altered acid-base status: the rules of engagement. *J Am Soc Nephrol* 2010; 21(6):920–923. doi:10.1681/ASN.2009121211
- Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol* 2007; 18(10):2649–2652. doi:10.1681/ASN.2007070792
- Rose BD. Metabolic alkalosis. In: *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 4th ed. New York, NY: McGraw-Hill, Health Professions Division; 1994:515.
- Calhoun DA, Jones D, Textor S, et al; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; 117(25):e510–e526. doi:10.1161/CIRCULATIONAHA.108.189141
- Koeppen BM, Stanton BA. Physiology of diuretic action. In: *Renal Physiology*. 5th ed. Philadelphia, PA: Elsevier Inc; 2013:167–178.
- Blumenfeld JD, Sealey JE, Schluskel Y, et al. Diagnosis and treatment of primary hyperaldosteronism. *Ann Intern Med* 1994; 121(11):877–885. PMID:7978702
- Kempers MJ, Lenders JW, van Outheusden L, et al. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. *Ann Intern Med*

- 2009; 151(5):329–337. pmid:19721021
11. Karagiannis A, Tziomalos K, Papageorgiou A, et al. Spironolactone versus eplerenone for the treatment of idiopathic hyperaldosteronism. *Expert Opin Pharmacother* 2008; 9(4):509–515. doi:10.1517/14656566.9.4.509
12. Sawka AM, Young WF, Thompson GB, et al. Primary aldosteronism: factors associated with normalization of blood pressure after surgery. *Ann Intern Med* 2001; 135(4):258–261. pmid:11511140
13. Haab F, Duclos JM, Guyenne T, Plouin PF, Corvol P. Renin secreting tumors: diagnosis, conservative surgical approach and long-term results. *J Urol* 1995; 153(6):1781–1784. pmid:7752315
14. Sabbadin C, Armanini D. Syndromes that mimic an excess of mineralocorticoids. *High Blood Press Cardiovasc Prev* 2016; 23(3):231–235. doi:10.1007/s40292-016-0160-5
15. Apostolakis JM, Caines LC. Apparent mineralocorticoid excess syndrome: a case of resistant hypertension from licorice tea consumption. *J Clin Hypertens (Greenwich)* 2016; 18(10):991–993. doi:10.1111/jch.12841
16. Glatt K, Garzon DL, Popovic J. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Spec Pediatr Nurs* 2005; 10(3):104–114. doi:10.1111/j.1744-6155.2005.00022.x
17. Findling JW, Raff H, Hansson JH, Lifton RP. Liddle's syndrome: prospective genetic screening and suppressed aldosterone secretion in an extended kindred. *J Clin Endocrinol Metab* 1997; 82(4):1071–1074. doi:10.1210/jcem.82.4.3862
18. Wang C, Chan TK, Yeung RT, Coghlan JP, Scoggins BA, Stockigt JR. The effect of triamterene and sodium intake on renin, aldosterone, and erythrocyte sodium transport in Liddle's syndrome. *J Clin Endocrinol Metab* 1981; 52(5):1027–1032. doi:10.1210/jcem-52-5-1027
19. 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. *Ann N Y Acad Sci* 2002; 970:134–144. pmid:12381548
20. Saruta T, Suzuki H, Handa M, Igarashi Y, Kondo K, Senba S. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. *J Clin Endocrinol Metab* 1986; 62(2):275–279. doi:10.1210/jcem-62-2-275
21. Clayton RN, Jones PW, Reulen RC, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. *Lancet Diabetes Endocrinol* 2016; 4(7):569–576. doi:10.1016/S2213-8587(16)30005-5
22. Baid SK, Rubino D, Sinaii N, Ramsey S, Frank A, Nieman LK. Specificity of screening tests for Cushing's syndrome in an overweight and obese population. *J Clin Endocrinol Metab* 2009; 94(10):3857–3864. doi:10.1210/jc.2008-2766
23. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008; 93(5):1526–1540. doi:10.1210/jc.2008-0125
24. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol* 2015; 7:281–293. doi:10.2147/CLEP.S44336
25. Tavares Bello C, van der Poest Clement E, Feelders R. Severe Cushing's syndrome and bilateral pulmonary nodules: beyond ectopic ACTH. *Endocrinol Diabetes Metab Case Rep* 2017; pii:17-0100. doi:10.1530/EDM-17-0100
26. Sathyakumar S, Paul TV, Asha HS, et al. Ectopic Cushing syndrome: a 10-year experience from a tertiary care center in southern India. *Endocr Pract* 2017; 23(8):907–914. doi:10.4158/EP161677.OR

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