CME MOC

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The devil is in the details: Approach to refractory hypokalemia

A man with multiple medical problems presents with a serum potassium level of 2.1 mmol/L without symptoms

A 71-year-old man was told by his primary care physician to go to the emergency department for evaluation of asymptomatic hypokalemia detected on outpatient laboratory testing. He had a history of coronary artery disease, hypertension, gout, and atrial fibrillation. He reported that his father and brother had well-controlled hypertension diagnosed in adulthood. He was a former smoker but denied alcohol consumption. Recently, he had been exercising daily and following a diet to lose weight. He had visited his primary care physician because of new-onset lower-extremity edema.

The patient said that he had intentionally lost 20 pounds over 2 months by decreasing his caloric intake, and that he had experienced no vomiting, diarrhea, or abdominal pain. He did not use over-the-counter medications or herbal supplements. His home medications included warfarin 7.5 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, lisinopril 20 mg daily, amiodarone 200 mg daily, and allopurinol 300 mg daily.

On physical examination, the patient was alert and oriented. He was not in any distress but appeared nervous. His temperature was 37.0°C (98.6°F), heart rate 84 beats per minute, blood pressure 186/100 mm Hg, respiratory rate 8 breaths per minute, and oxygen saturation 99% while breathing oxygen at 4 L/minute by nasal cannula. He had central obesity, with a body mass index of 34 kg/m^2. His heart rhythm was irregular, his lungs were clear to auscultation without crackles or wheezing, and gastrointestinal and neurologic examinations were unremarkable.

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His initial serum potassium level was 2.1 mmol/L (reference range 3.5–5.0 mmol/L). Other initial laboratory values are listed in **Table 1**.

He was admitted to the hospital and received a total of 230 mmol of potassium intravenously and by mouth over the next 20 hours, but his serum potassium level increased to only 2.9 mmol/L. Therefore, the nephrology service was consulted to evaluate his refractory hypokalemia.

METABOLIC DISTURBANCES REVIEWED

1 What metabolic disturbance does the patient have?

- ☐ Metabolic alkalosis with respiratory acidosis
- ☐ Mixed metabolic and respiratory alkalosis
- ☐ Triple disorder with metabolic alkalosis, metabolic acidosis, and respiratory alkalosis
- ☐ Compensated metabolic alkalosis

Analyzing an acid-base disturbance is a 5-step process.

Step 1: Look at the pH. Our patient's arterial pH was 7.55, which, being higher than 7.45, shows a state of alkalemia.

Step 2: Determine if the primary process is metabolic or respiratory. In primary metabolic alkalosis, the serum bicarbonate level is high—and our patient's bicarbonate level was significantly elevated at more than 45 mmol/L (reference range 23–32 mmol/L). On the other hand, in primary respiratory alkalosis (as can occur during hyperventilation), the partial pressure of carbon dioxide (Pco_2) is low—but our patient's breathing was slow and his Pco_2 was elevated, reflecting a compensatory process (see **Step 4**, below).

Step 3: Calculate the anion gap. Subtract the sum of the concentrations of the anions chloride and bicarbonate from the concentration of the most abundant cation, sodium. Importantly, the anion gap should be adjusted for the effect of an abnormal serum albumin concentration. The difference between the normal and the measured serum albumin concentrations in grams per deciliter is multiplied by 2.5, and the result is added to the calculated anion gap. In our patient's case, the anion gap adjusted for albumin was 5.25 mmol/L (reference range 8–16 mmol/L). The absence of an elevated anion gap ruled out concomitant metabolic acidosis.

Step 4: Assess compensation. In compensating for metabolic alkalosis, the breathing can slow down, and the Pco_2 can rise by as much as 0.7 mm Hg, from a normal of 40 mm Hg for every 1-mmol/L rise in the plasma bicarbonate concentration (from a normal level of 24 mmol/L). Therefore, as our patient's bicarbonate level was 45 mmol/L (21 mmol/L above normal), his Pco_2 could increase by about 15 mm Hg to approximately 55 mm Hg—for a measured value of 54 mm Hg. Note that this compensatory process of carbon dioxide retention involves slowing the respiratory rate, which is not always achievable. Also, this hypoventilation can result in hypoxemia, which was observed in our patient.

Step 5: Calculate the delta gap in cases of metabolic acidosis. Our patient had metabolic alkalosis, not acidosis, and therefore did not need this step.

In conclusion, the patient had metabolic alkalosis with appropriate respiratory compensation.[1]

TABLE 1

The patient's laboratory values on admission

Test	Results[a]	Reference range
Sodium	140 mmol/L	132–148 mmol/L
Potassium	**2.1 mmol/L**	3.5–5.0 mmol/L
Chloride	**93 mmol/L**	98–111 mmol/L
Bicarbonate	**> 45 mmol/L**	23–32 mmol/L
Blood urea nitrogen	**30 mg/dL**	10–25 mg/dL
Creatinine	1.11 mg/dL	0.7–1.4 mg/dL
Calcium	**8.0 mg/dL**	8.4–10.5 mg/dL
Albumin	**2.7 g/dL**	3.5–5.0 g/dL
Hemoglobin A1c	**6.8%**	< 5.7%
Hemoglobin	14.5 g/dL	12–16 g/dL
White blood cell count	**14.3 × 10^9/L**	3.7–11.0 × 10^9/L
Platelet count	**79 × 10^9/L**	140–400 × 10^9/L
Alanine aminotransferase	**79 U/L**	0–45 U/L
Aspartate aminotransferase	**81 U/L**	7–40 U/L
Alkaline phosphatase	129 U/L	40–150 U/L
Bilirubin, total	1.4 mg/dL	0–1.5 mg/dL
Arterial blood gasses		
pH	**7.55**	7.35–7.45
Pco_2	**54 mm Hg**	35–45 mm Hg
Po_2	**34 mm Hg**	75–100 mm Hg
Bicarbonate	**47 mmol/L**	18–23 mmol/L

[a] Abnormal results are shown in bold.

FURTHER EVALUATION OF METABOLIC ALKALOSIS

2 What is the best next step to further evaluate this patient's metabolic disorder?

- ☐ Random urine chloride measurement
- ☐ Random urine sodium measurement
- ☐ Random urine potassium measurement
- ☐ Random urine ammonium measurement

Metabolic alkalosis should first be evaluated by obtaining a random urine chloride measurement (**Figure 1**). This helps classify metabolic alkalosis as either volume-responsive (urine chloride < 20 mmol/L) or volume-resistant (urine chloride ≥ 20 mmol/L).[1]

Urine chloride is more accurate than urine sodium as an indicator of intravascular volume depletion because chloride has a negative charge. In states of hypovolemia, sodium and chloride are reabsorbed from the urine as a consequence of activation of the renin-angiotensin-aldosterone system. In metabolic alkalosis, the kidneys respond by excreting bicarbonate in the urine. The negative charge of bicarbonate, particularly in early stages of volume-depleted metabolic alkalosis, drags the

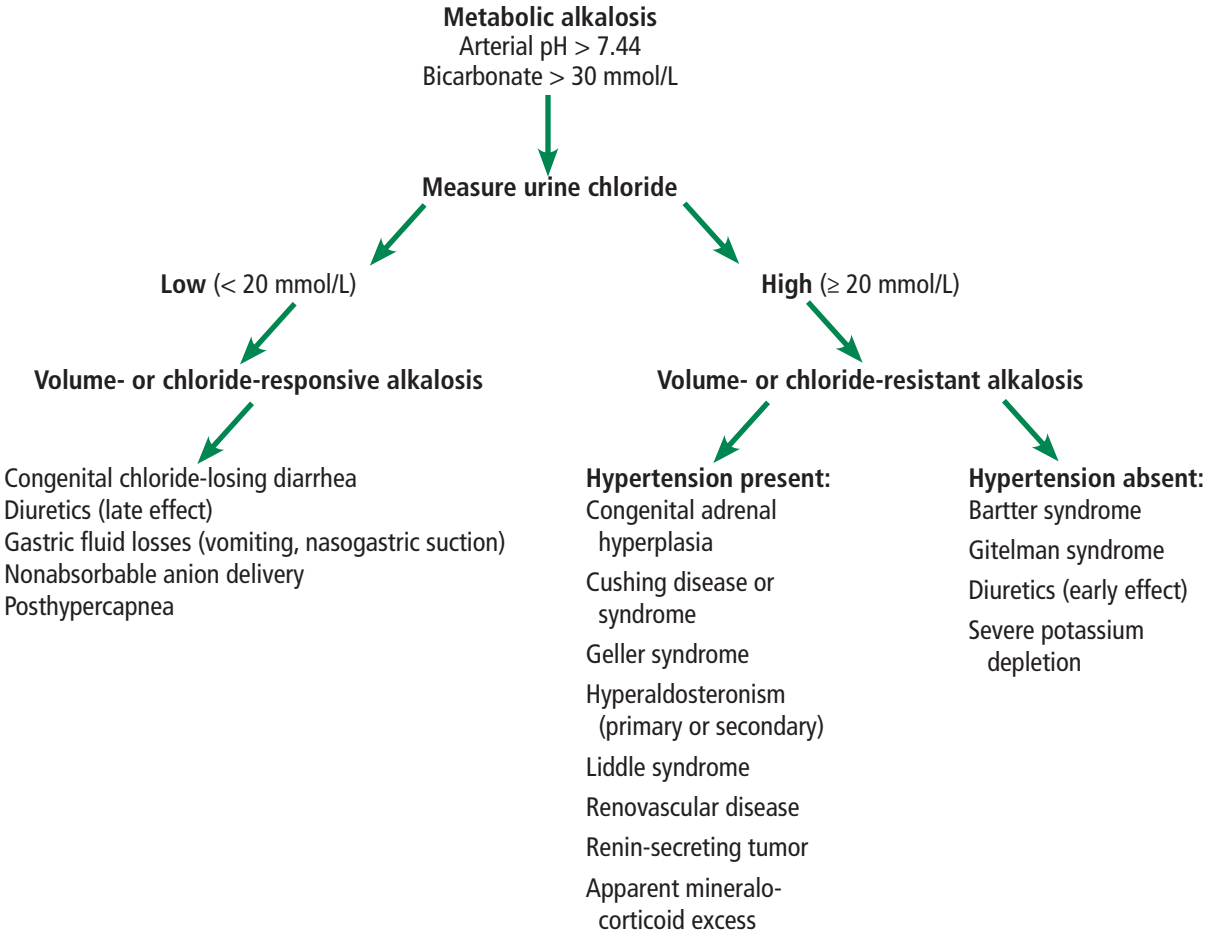

Figure 1. Metabolic alkalosis should first be evaluated by obtaining a random urine chloride. This step helps classify it as volume-responsive (urine chloride < 20 mmol/L) or volume-resistant (urine chloride ≥ 20 mmol/L). The latter is further divided based on the presence or absence of hypertension.

positively charged ions sodium and potassium into the urine to maintain electroneutrality. Therefore, urine sodium and potassium levels are elevated in the first 24 to 72 hours of volume depletion, but after 72 hours they drop.

Urine ammonium is measured when evaluating non-gap metabolic acidosis but has no role in states of alkalosis.[2]

CASE CONTINUED: RESULTS OF FURTHER TESTING

Results of additional testing (**Table 2**) showed a urine chloride level of 32 mmol/L, indicating his metabolic alkalosis was volume-resistant.

Further, his urine potassium level was 68 mmol/L and his urine creatinine level was 80 mg/dL. (ie, 7.04 mmol/L) Therefore, his urine potassium-to-creatinine ratio was 9.66—and values greater than 1.5 indicate urinary loss of potassium.

Several days later, the patient's renin level was measured and was normal, and his aldosterone level was low. Note that he was taking lisinopril at home. Angiotensin-converting enzyme (ACE) inhibitors such as lisinopril block production of angiotensin II, thereby interrupting the negative feedback loop of the renin-angiotensin-aldosterone cascade and stimulating renin synthesis.[3] However, a state of hypercortisolemia will suppress renin levels, which in our patient might appear artificially normal due to the concomitant use of an ACE inhibitor.

CAUSES OF VOLUME-RESISTANT METABOLIC ALKALOSIS WITH LOW RENIN AND ALDOSTERONE

3 All of the following conditions can cause volume-resistant metabolic alkalosis with low renin and low aldosterone levels except which one?

- ☐ Liddle syndrome
- ☐ Apparent mineralocorticoid excess
- ☐ Cushing syndrome
- ☐ Glucocorticoid-remediable aldosteronism

Liddle syndrome is an autosomal-dominant condition characterized by hyperactivity of the epithelial sodium channel. More than 30 variants of the genes that code for the 4 subunits of this channel have been described, and the clinical features of Liddle syndrome can differ significantly, as it has variable penetrance.[4,5]

The epithelial sodium channel is found in the principal cell of the cortical collecting duct of the distal nephron. If activity of this channel is increased, the abnormality will resemble a high-aldosterone state by causing excessive sodium reabsorption and potassium excretion. The high sodium load leads to volume expansion and hypertension.[1,2] Therefore, this syndrome usually presents as early-onset hypertension, hypokalemia, volume-resistant metabolic alkalosis, and a low-renin and low-aldosterone state, since these hormone levels are suppressed. Due to its variable penetrance, the severity of the hypertension and the age of onset can differ.[4,5]

Apparent mineralocorticoid excess is an autosomal-recessive disease caused by a deficiency of the enzyme 11-beta hydroxysteroid dehydrogenase type 2.[6,7] This enzyme converts cortisol to one of its inactive metabolites, cortisone, in aldosterone target organs such as the collecting tubules in the kidney.[1]

Cortisol and aldosterone have the same affinity for the mineralocorticoid receptor, but cortisol circulates in the system in a higher concentration (**Figure 2**). Therefore, this enzyme limits cortisol from acting as the major endogenous mineralocorticoid.[1,2] Licorice and medications like posaconazole can also inhibit this enzyme, resulting in a state of excess cortisol that activates the mineralocorticoid receptors and clinically resembles primary hyperaldosteronism.[1,6] Volume-resistant metabolic alkalosis, hypokalemia, low renin, and low aldosterone levels are characteristic of this syndrome.[7]

TABLE 2
Additional workup

Tests	Results[a]	Reference range
Urine potassium, random	68 mmol/L	17.0–99.0 mmol/L
Urine chloride, random	32 mmol/L	30–260 mmol/L
Urine creatinine, random	80 mg/dL	40–278 mg/dL
Serum renin	2.17 ng/mL	0.25–5.82 ng/mL
Serum aldosterone	**< 1 ng/dL**	3–16 ng/dL

[a] Abnormal results are shown in bold.

Cushing syndrome is a state of cortisol excess caused by ectopic production of adrenocorticotropic hormone (ACTH).[8,9] ACTH stimulates the zona fasciculata of the adrenal gland, leading to excessive production of cortisol.[8] The excess cortisol overwhelms the 11-beta hydroxysteroid dehydrogenase enzyme in the distal tubules and activates the mineralocorticoid receptors, producing a clinical picture of primary hyperaldosteronism.[1] The most common sources of ectopic ACTH production include small-cell lung cancer and carcinoid tumors.[9,10] As described above, this excessive activation of the mineralocorticoid receptor presents with volume-resistant metabolic alkalosis with low renin and low aldosterone levels.

Glucocorticoid-remediable aldosteronism is an autosomal-dominant condition in which chimeric gene duplication leads to crossover between the 11-beta hydroxylase and aldosterone synthase genes.[11] As a result, aldosterone is produced ectopically in the zona fasciculata solely under the stimulation of ACTH.[2,11] The clinical picture is characterized by early-onset severe hypertension, and cerebrovascular and cardiovascular complications with a mean age of 32 at the time of the initial event.[11]

Even though this is another cause of volume-resistant metabolic alkalosis, glucocorticoid-remediable aldosteronism is a mineralocorticoid-excess state in which aldosterone

Potassium infusions and supplements failed to raise his potassium level

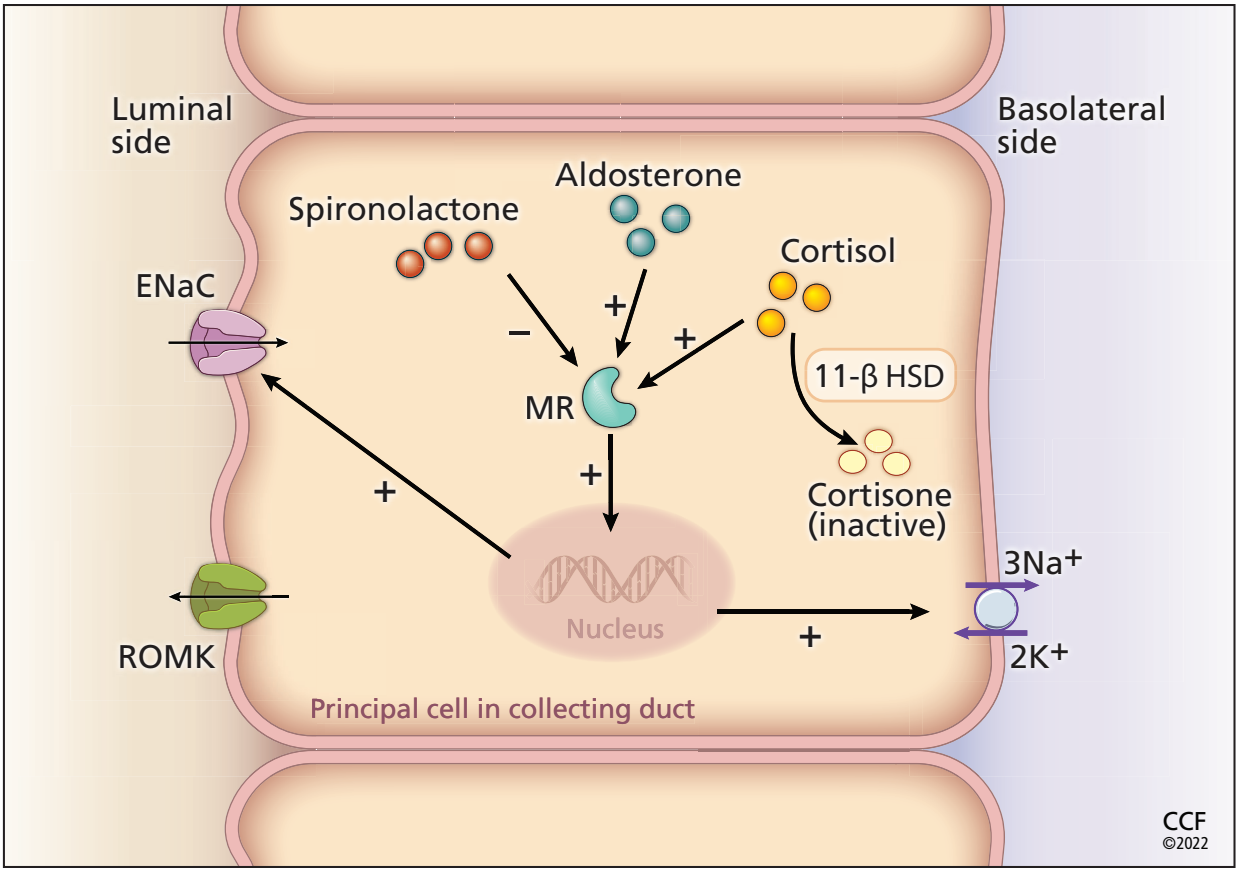

Figure 2. Processes of mineralocorticoid excess and effect of spironolactone. In the principal cells in the collecting ducts of the kidney, activation of the mineralocorticoid receptor (MR) increases the transcription, translation, and insertion of more epithelial sodium channels (ENaC) in the luminal side. Cortisol and aldosterone have the same affinity for the mineralocorticoid receptor, but aldosterone is present in higher concentrations. Activation of the mineralocorticoid receptor stimulates a cascade of intracellular reactions that results in increased expression of the epithelial sodium channel. Spironolactone blocks the mineralocorticoid receptor. The enzyme 11-β hydroxysteroid dehydrogenase (HSD) type 2 converts cortisol to its inactive metabolite, cortisone. This enzyme can be absent in apparent mineralocorticoid excess, or it can be inhibited by licorice or posaconazole. Notably, the increased number of epithelial sodium channels leads to sodium (Na^+) reabsorption from the tubular lumen. To maintain electroneutrality, another positive ion (K^+) is secreted into the tubular lumen through the renal outer medullary potassium channel (ROMK).

levels are elevated and renin is suppressed. Therefore, this is the correct answer to the question above. Of importance, hypokalemia is uncommon in glucocorticoid-remediable aldosteronism, and when it occurs, it is usually triggered by a potassium-wasting diuretic agent.[2,11]

The diagnosis of this condition is based on confirming that aldosterone is suppressed when glucocorticoids are given, on genetic testing, or on detecting high levels of C-18 oxidation products of cortisol in the urine.[2,11]

CASE CONTINUED: A CANCER DIAGNOSIS

Liddle syndrome is characterized by early-onset hypertension and a strong family history, making this condition less likely in our patient. Along the same lines, the inherited form of apparent mineralocorticoid excess presents in early childhood, while its acquired form, caused by inhibition of the enzyme 11-beta hydroxysteroid dehydrogenase type 2, is triggered by medications such as antifungals or by licorice, which our patient was not consuming.

Because Cushing syndrome was strongly suspected in this patient, further evaluation was pursued (**Table 3**), and ultrasonography of the liver was performed to evaluate the patient's elevated aminotransferase levels and thrombocytopenia. Multiple hepatic masses were detected, the largest being 5 cm. This was followed by computed tomography of the chest, abdomen, and pelvis, which revealed a right suprahilar pulmonary nodule measuring 2.7 cm, bilateral diffuse adrenal nodularity (the probable source of his excess cortisol), and liver and pancreatic masses. Magnetic resonance imaging did not show any metastases in the brain or pituitary gland. Liver biopsy revealed metastatic small-cell lung cancer.

TABLE 3

Further additional workup

Tests	Results[a]	Reference range
Cortisol, AM level	**125 µg/dL**	6–26 µg/dL
24-hour urinary cortisol excretion	**16,080 µg/24 hours**	4–50 µg/24 hours
Adrenocorticotropic hormone	**1,140 pg/mL**	6–50 pg/mL

[a] Abnormal results are shown in bold.

ANTIHYPERTENSIVE THERAPY IN HYPERMINERALOCORTICOID STATES

4 Which medication would be indicated to address this patient's hypertension?

- ☐ Spironolactone
- ☐ Verapamil
- ☐ Losartan
- ☐ Aliskiren

Spironolactone is a synthetic steroid that competes with aldosterone. It also has affinity for steroid receptors, specifically those of progesterone and androgen systemically.[12]

In the kidney, spironolactone is delivered through the blood to the distal nephron, where it penetrates the basolateral membrane and binds the mineralocorticoid receptor, located in the cytosol (**Figure 2**).[13] When aldosterone activates this receptor, a cascade of intracellular reactions is triggered, culminating in a decrease in degradation of the epithelial sodium channel.[14] As a result, aldosterone increases sodium reabsorption and volume expansion, and its antagonist, spironolactone, blocks these effects.[13,14]

Importantly, in the absence of mineralocorticoid excess, other potassium-sparing diuretics such as amiloride (an epithelial sodium channel blocker) are preferred to minimize renal losses of potassium, as they are better tolerated.

Verapamil is a nondihydropyridine calcium channel blocker that causes peripheral vasodilation and cardiac depression.[15] It is a therapeutic option for hypertension, but it does not affect the mineralocorticoid pathway.

Losartan is a selective inhibitor of the angiotensin II receptor. Angiotensin II induces vasoconstriction and the release of hormones like aldosterone, as well as catecholamines and arginine vasopressin.[16] Consequently, angiotensin II receptor blockers (ARBs) lower aldosterone levels and, due to negative feedback, they increase renin and angiotensin II levels.[3]

Even though ARBs are excellent therapeutic options in states of excess renin-angiotensin-aldosterone activation, specific conditions of mineralocorticoid excess are better addressed by targeted therapy with mineralocorticoid receptor antagonists such as spironolactone.[17] Furthermore, the hypertension in Cushing syndrome is not mediated by an excess of aldosterone but by excess cortisol.[8]

Aliskiren is a direct renin inhibitor that binds to renin at its active site, thereby stopping the cleavage of angiotensinogen that produces angiotensin I. In normal conditions, angiotensin I is converted by ACE to angiotensin II. Therefore, aliskiren blocks the renin-angiotensin-aldosterone system at an earlier stage than ACE inhibitors, ARBs, or spironolactone.[18] As mentioned above, Cushing syndrome causes hypertension through an excess of cortisol, which directly activates the mineralocorticoid receptor.

The patient was treated with spironolactone, and his hypertension and hypokalemia improved

CASE CONCLUSION

The patient was treated with spironolactone, and his hypertension and hypokalemia improved. Weeks later, he was readmitted to

start chemotherapy and received etoposide and carboplatin. Because the cancer was advanced and unresectable, adrenalectomy to treat the hypercortisolemia was ruled out, and the 11-beta hydroxylase inhibitor metyrapone was added to his regimen with the goal of decreasing the conversion of 11-deoxycortisol to cortisol.

Unfortunately, the patient developed septic shock and kidney failure secondary to disseminated aspergillosis and died less than 2 months after his initial presentation with asymptomatic, refractory hypokalemia.

TEACHING POINTS

- Severe hypokalemia (serum potassium level < 3 mmol/L) or symptomatic hypokalemia warrants prompt repletion and closer monitoring of serum levels to determine response to therapy. A lower serum potassium threshold should be applied for patients with heart disease, due to increased risk for arrhythmias, as in our patient.
- The expected respiratory compensation for metabolic alkalosis is a 0.7-mm Hg increase in P_{CO_2} from a normal P_{CO_2} of 40 mm Hg for every 1-mmol/L rise in the plasma bicarbonate concentration from a normal level of 24 mmol/L.
- Chloride is the best urine electrolyte to measure to evaluate volume status in metabolic alkalosis, allowing it to be classified as either volume-responsive (urine chloride < 20 mmol/L) or volume-resistant (urine chloride ≥ 20 mmol/L).
- Liddle syndrome, apparent mineralocorticoid excess, and Cushing syndrome can cause volume-resistant metabolic alkalosis with low renin and low aldosterone levels.
- Spironolactone, a mineralocorticoid receptor antagonist, is the drug of choice for hypertension in states of mineralocorticoid excess.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Rose BD, Post TW**. Clinical Physiology of Acid-Base and Electrolyte Disorders. 5th ed. New York, NY: McGraw Hill; 2001.
2. **Kamel SK, Halperin ML**. Fluid, Electrolyte, and Acid-base Physiology: A Problem-based Approach. 5th ed. Philadelphia, PA: Elsevier; 2017:393–432.
3. **Chen L, Kim SM, Eisner C, et al**. Stimulation of renin secretion by angiotensin II blockade is Gsalpha-dependent. J Am Soc Nephrol 2010; 21(6):986–992. doi:10.1681/ASN.2009030307
4. **Tetti M, Monticone S, Burrello J, et al**. Liddle syndrome: review of the literature and description of a new case. Int J Mol Sci 2018; 19(3):812. doi:10.3390/ijms19030812
5. **Enslow BT, Stockand JD, Berman JM**. Liddle's syndrome mechanisms, diagnosis and management. Integr Blood Press Control 2019; 12:13–22. doi:10.2147/IBPC.S188869
6. **Pandit A, Schlondorff J**. Posaconazole-induced apparent mineralocorticoid excess. Kidney Int Rep 2020; 5(12):2379–2382. doi:10.1016/j.ekir.2020.09.025
7. **Funder JW**. Apparent mineralocorticoid excess: research as an art form. Endocrine 2020; 70(3):439–440. doi:10.1007/s12020-020-02488-x
8. **Mazzocchi G, Malendowicz LK, Rebuffat P, Robba C, Gottardo G, Nussdorfer GG**. Short- and long-term effects of ACTH on the adrenal zona glomerulosa of the rat. A coupled stereological and enzymological study. Cell Tissue Res 1986; 243(2):303–310. doi:10.1007/BF00251044
9. **Liddle GW, Island DP, Ney RL, Nicholson WE, Shimizu N**. Nonpituitary neoplasms and Cushing's syndrome. Ectopic "adrenocorticotropin" produced by nonpituitary neoplasms as a cause of Cushing's syndrome. Arch Intern Med 1963; 111:471–475. doi:10.1001/archinte.1963.03620280071011
10. **Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK**. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 2005; 90(8):4955–4962. doi:10.1210/jc.2004-2527
11. **Halperin F, Dluhy RG**. Glucocorticoid-remediable aldosteronism. Endocrinol Metab Clin North Am 2011; 40(2):333–viii. doi:10.1016/j.ecl.2011.01.012
12. **Delyani JA**. Mineralocorticoid receptor antagonists: the evolution of utility and pharmacology. Kidney Int 2000; 57(4):1408–1411. doi:10.1046/j.1523-1755.2000.00983.x
13. **Wile D**. Diuretics: a review. Ann Clin Biochem 2012; 49(Pt 5): 419–431. doi:10.1258/acb.2011.011281
14. **Karim A**. Spironolactone: disposition, metabolism, pharmacodynamics, and bioavailability. Drug Metab Rev 1978; 8(1):151–188. doi:10.3109/03602537808993782
15. **Midtbø K, Hals O, Lauve O, van der Meer J, Storstein L**. Studies on verapamil in the treatment of essential hypertension: a review. Br J Clin Pharmacol 1986; 21(suppl 2):165S–171S. doi:10.1111/j.1365-2125.1986.tb02867.x
16. **Barreras A, Gurk-Turner C**. Angiotensin II receptor blockers. Proc (Bayl Univ Med Cent) 2003; 16(1):123–126. doi:10.1080/08998280.2003.11927893
17. **Seifarth C, Trenkel S, Schobel H, Hahn EG, Hensen J**. Influence of antihypertensive medication on aldosterone and renin concentration in the differential diagnosis of essential hypertension and primary aldosteronism. Clin Endocrinol (Oxf) 2002; 57(4):457–465. doi:10.1046/j.1365-2265.2002.01613.x
18. **Allikmets K**. Aliskiren—an orally active renin inhibitor. Review of pharmacology, pharmacodynamics, kinetics, and clinical potential in the treatment of hypertension. Vasc Health Risk Manag 2007; 3(6):809–815. pmid:18200801

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