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The Case | A 62-year-old man with severe alkalosis

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Table 1 | Laboratory parameters in blood and urine on admission

Parameter	Previous[a]	Presentation	Reference range
Serum			
Sodium, mmol/l	139	130	135–145
Chloride, mmol/l		67	97–107
Potassium, mmol/l	5.2	2.0	3.5–5.0
Magnesium, mmol/l		0.87	0.7–1.05
Urea, mmol/l		19.0	2.5–6.4
Creatinine, μmol/l	129	160	64–104
Osmolality, mOsm/kg		299	275–300
Albumin, g/l		30	35–50
pH	7.40	7.61	7.35–7.45
pCO_2, mm Hg	47	55	35–48
pO_2, mm Hg		77	75–100
Bicarbonate, mmol/l	28	54	21–28
Renin activity, ng/ml/h		55.0	0.3–5.5
Aldosterone, pmol/l		334	56–660
Urine			
Sodium, mmol/l		7	—
Chloride, mmol/l		<10	—
Potassium, mmol/l		38	—
Creatinine, mmol/l		10.4	—
pH		5.5	—
Osmolality, mOsm/kg		351	—
Protein, g/l		0.84	—
Transtubular potassium gradient[b]		16	

[a]Measured approximately 3 weeks before presentation.
[b]Formula: (serum osmolality × urine potassium)/(serum potassium × urine osmolality).

A 62-year-old obese Caucasian man (body mass index 46 kg/m^2) presented to the emergency room with dyspnea. He had a history of chronic obstructive pulmonary disease (COPD) related to smoking (forced expiratory volume in 1 s was 0.90 l, Tiffeneau index 33%). His medication consisted of inhalation drugs (salmeterol, fluticasone, and tiotropium) and antihypertensive drugs (perindopril 4 mg per day, spironolactone 50 mg per day). Three weeks before admission, his pulmonologist had started furosemide (40 mg per day) because of peripheral edema. No other abnormalities were noted at that time. An arterial blood gas during this previous visit showed the following: pH 7.4, pCO_2 47 mm Hg, and bicarbonate 28 mmol/l.

On physical examination in the emergency room, he was hypertensive (180/110 mm Hg) and had severe pitting edema in his lower extremities. No pulmonary rales or elevated central venous pressure were noted. During assessment in the emergency room, the patient had two runs of ventricular tachycardia. His laboratory results are shown in Table 1 and revealed severe alkalosis. A chest X-ray showed pulmonary emphysema without an infiltrate. Transthoracic echocardiography showed normal atrial dimensions, normal systolic function, normal heart valves, and a normal vena cava inferior diameter.

The presentation and the laboratory results raise the following questions: What type of acid–base disorder does the patient have? What are the possible causes of the acid–base disorder? How would you treat this patient and why?

What is the cause of severe alkalosis in this patient?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Severe metabolic alkalosis due to chloride and potassium depletion

The presence of chloride depletion metabolic alkalosis was suggested by the very low serum and urine chloride concentrations. Furthermore, there was also evidence of potassium depletion. Although alkalosis can cause hypokalemia through redistribution, severe hypokalemia in combination with inappropriately elevated urine potassium suggested renal potassium loss. The transtubular potassium gradient revealed an aldosterone-like effect. However, serum aldosterone was not increased, suggesting pseudohyperaldosteronism. The normal serum aldosterone, normal cardiac ultrasound, and the presence of hypertension rendered both volume contraction and heart failure unlikely. Although the use of furosemide could explain some of these findings, it appeared unusual for such a low dose of furosemide to cause such severe perturbations.

Therefore, we returned to the patient and his family the day after admission. This revealed that the patient had been using several tablets of furosemide per day, but that he had discontinued using spironolactone. Moreover, he had been using $\sim$300 g of licorice daily. This new information provided a better explanation for the severity of the metabolic alkalosis, which was likely due to severe chloride and potassium depletion because of overzealous use of loop diuretics and licorice. Interestingly, in animals, chloride depletion alkalosis can also cause a volume-independent reduction in glomerular filtration rate,[1] as was also present in this patient. In addition, as illustrated by the blood gas before admission, he likely had chronic mild respiratory acidosis with metabolic compensation, which by itself also promotes renal chloride loss.[2] Renin activity was likely increased by loop diuretics and perindopril, whereas perindopril, licorice, and severe hypokalemia may have suppressed aldosterone.

Licorice contains glycyrrhizic acid, which inhibits the enzyme 11β-hydroxysteroid dehydrogenase type 2 that normally prevents cortisol from activating the mineralocorticoid receptor. The low urine sodium chloride concentration suggested a post-diuretic state or active sodium chloride reabsorption due to licorice. Chloride depletion impedes bicarbonate secretion via the chloride–bicarbonate exchanger in the distal nephron.[3] Potassium depletion and an aldosterone effect will sustain alkalosis by activating H^+/K^+-ATPase and by promoting ammoniogenesis.[3] This case illustrates that chloride depletion in the absence of volume contraction can cause severe alkalosis. We therefore agree with a recent editorial proposing to replace the term 'contraction alkalosis' by 'chloride depletion metabolic alkalosis'.[3] However, treatment should not only rely on chloride repletion, but also on replacing the cation lost with chloride, namely potassium, as hypokalemia caused the most threatening symptoms (arrhythmia). Therefore, this patient was treated with potassium chloride, acetazolamide, and hydrochloric acid. These measures led to a normalization of serum chloride, bicarbonate, potassium, and creatinine. We emphasize that both hydrochloric acid and acetazolamide should be used with caution because they can cause hemolysis and kaliuresis, respectively. The patient's dyspnea was explained by an exacerbation of COPD with possible contributions of hypokalemia (muscle weakness) and alkalosis (respiratory depression). The cause of his edema remained unclear, but may have been idiopathic or related to diuretic or licorice abuse.

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