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Case Report

Case report: a rare cause of metabolic alkalosis

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Abstract
A case of a 66-year-old white man with recent onset of oedema, hypertension, metabolic alkalosis and profound hypokalaemia is described. The initial laboratorial workup showed that urinary chloride concentration and potassium excretion were increased, suggesting a state of hyperaldosteronism. Nonetheless, renin activity was low and aldosterone levels were normal. The metabolic alkalosis seen in this case was due to a rare cause, the ectopic adrenocorticotropic hormone syndrome. A literature review in the subject is presented.

Keywords: ectopic adrenocorticotropic hormone syndrome; hypokalaemia; metabolic alkalosis

Background

Metabolic alkalosis has an extensive differential diagnosis. Diagnosis requires a systematic approach in order to differentiate simple causes from potential life-threatening conditions.

Case report

A 66-year-old white male presented to our hospital with recent onset of oedema and weight gain of 8 kg. The patient also reported fatigue, somnolence and increased thirst. He had no symptoms of dyspnoea, cough, fever or urinary abnormalities. His medical history included a 5-year history of diabetes mellitus, hypertension and hypothyroidism. He was a smoker and was on furosemide, metformin, glicazide, insulin, levothyroxine and sinvastatin. On physical examination, he was seen to be lethargic, with no neurological focal signs. Blood pressure was 180/80 mmHg, heart rate was 84 b.p.m. and body temperature was normal. A diffused oedema was noticed with no signs of ascites or pleural effusion. Heart, lung and abdomen examination were unremarkable.

Table 1 shows the initial laboratory workup. Hepatitis serology was negative, complement levels were normal and glycated haemoglobin was 9.3%. Renin activity was <0.4 μg/mL/h (0.4–0.7 μg/mL/h) and serum aldosterone was 0.20 nmol/L (0.05–0.44 nmol/L, rest). Fundoscopy showed no signs of hypertensive or diabetic retinopathy. An electrocardiogram presented a long-QT interval, U wave and frequent supraventricular extrasystoles. Chest X-ray was normal and echocardiography revealed no significant abnormalities with normal systolic and diastolic function.

Evaluation and diagnosis

During the first 24 h of hospitalization, the patient's neurological status deteriorated, with the onset of delirium. Despite the initial correction of his electrolyte abnormalities, both hypokalaemia and metabolic alkalosis were significantly worse. He was admitted to the intensive care unit and received oral acetazolamide, spironolactone and intravenous insulin. He was also started on intravenous chlorhydric acid (HCl 18.6%), and has subsequently shown a marked improvement in metabolic alkalosis.

Neuroimaging was normal, but abdominal magnetic resonance revealed an enlarged liver with multiple nodules. Adrenocorticotropic hormone (ACTH) was 61.2 pmol/L (up to 10.1 pmol/L) and cortisol was 2373 nmol/L (149–690 nmol/L). Hepatic biopsy (Figure 1) revealed a neoplasia composed of small cells, with scanty cytoplasm and a hyperchromatic nuclei. Immunohistochemistry revealed moderate to strong expression of chromogranin A and thyroid transcription factor-1, positivity for synaptophysin, rare immunexpression of keratin 7 and uniform weak immunexpression of CD15, with negative expression for other markers. Overall, histology and immunohistochemistry were comparable with the diagnosis of lung neuroendocrine carcinoma (undifferentiated small-cell carcinoma). Serum chromogranin A was 107.1 μg/L (up to 36.4 μg/L).

After diagnosis, the patient was started on ketoconazole, from which he showed rapid improvement of the hypercortisolism state. In addition, chemotherapy was initiated, including dexamethasone, cisplatin and irinotecan. Ten days after ketoconazole initiation, urine analysis was normal and 24-h proteinuria decreased to 0.33 g/24 h.

Table 1. Initial laboratory workup[a]

	Result	Range
Urea	21.8	3.6–17.9 mmol/L
Creatinine	88.4	61.9–115 μmol/L
Ionized calcium	0.74	1.11–1.40 mmol/L
Sodium	142	136–145 mmol/L
Potassium	1.7	3.5–4.5 mmol/L
Magnesium	0.7	0.65–1.07 mmol/L
Chloride	98.0	98–107 mmol/L
pH	7.6	7.33–7.45
Bicarbonate	49.0	23–27 mmol/L
Base excess	22.3	(−)3.0–(+)3.0
Glycaemia	12.7	3.9–5.5 mmol/L
Haemoglobin	130	135–175 g/L
Haematocrit	40.4	39–50%
Leucocyte	9.9	3.5–10.5 × 10^9/L
Platelet count	102	150–400 × 10^9/L
Albumin	32.8	39–53 g/L
Gamma globulin	5.5	6–16 g/L
Creatine kinase	1550	38–174 U/L
Aspartate aminotransferase	48	<37 U/L
Alanine aminotransferase	44	<41 U/L
Gamma glutamyl transferase	46	12–73 U/L
TSH	<0.05	0.45–4.5 mIU/L
Free T4 (thyroxine)	33.5	11.6–21.9 pmol/L
Urine analysis		
Density/pH	6/1015	
Leucocytes	20 000	<20 000/mL
Erythrocytes	20 000	<10 000/mL
Proteins	3.65 g	Negative
Glucose	>55.5 mmol/L	Negative
24-h proteinuria	4.18	<0.15 g/24 h
24-h potassium excretion	92	25–125 mmol/24 h
24-h chloride excretion	233	110–250 mmol/24 h
24-h sodium excretion	282	40–220 mmol/24 h

[a]TSH, thyroid stimulating hormone.

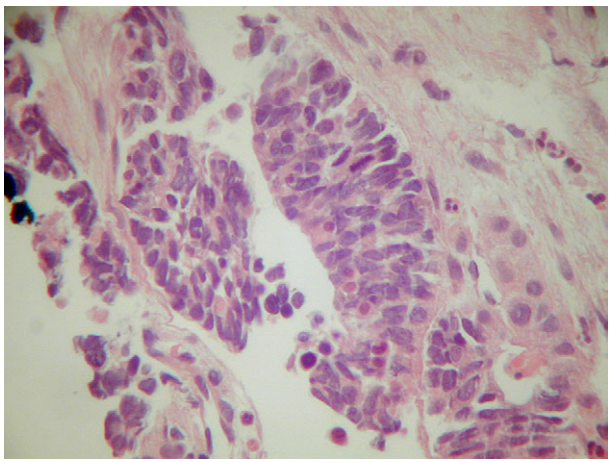

Fig. 1. Histologic sections of liver needle biopsy showing a neoplasia composed of small cells, with scanty cytoplasm and hyperchromatic nuclei. Immunohistochemistry confirmed neuroendocrine differentiation by positivity of chromogranin A and synaptophysin, besides cytokeratins.

Eight days after chemotherapy initiation, the patient presented fever and leucopenia. Antibiotics and granulocyte colony-stimulating factor were started but the patient presented a sudden cardiac arrest, with no response to resuscitation.

Discussion

Metabolic alkalosis has an extensive differential diagnosis [1]. It is classified according to three mechanisms: (i) loss of hydrogen, further classified into gastrointestinal loss (vomiting, nasogastric suction), renal loss (diuretic use, mineralocorticoid excess, chronic hypercapnia, hypercalcaemia, Bartter and Gitelman Syndromes) or due to hydrogen shift; (ii) retention of bicarbonate, as occurs in massive blood transfusions and (iii) contraction alkalosis, characterized by loss of fluid containing Cl^- and no, or little, HCO_3^- (diuretics).

In the present case, the cardinal signs were severe metabolic alkalosis, profound hypokalaemia and oedema. Initial laboratory workup showed that urinary chloride concentration was increased, suggesting that a renal mechanism was involved. In addition, 24-h potassium excretion was high considering a low serum potassium. Although furosemide could partially explain these findings, the magnitude of the laboratory abnormalities suggested that other aetiology was involved. There are three mechanisms by which hyperaldosteronism and hypokalaemia may possibly influence H^+ secretion and HCO_3^- reabsorption: by stimulating the intracellular shift of H^+; by stimulating distal H^+- K^+-ATPase and H^+-ATPase pumps and by reducing Cl^- reabsorption in the distal nephron. However, in the present

case, renin activity was low and aldosterone levels were normal.

A hypercortisolism state was then considered. Cortisol has an important affinity to the aldosterone receptor. In normal conditions, excessive activation is prevented by the activity of 11β-hydroxysteroid dehydrogenase in the renal tubule. In hypercortisolism states, saturation of the enzyme activity occurs and features of hyperaldosteronism appear. In addition, ACTH may also cause a transient rise in aldosterone secretion. This effect could explain the level of aldosterone found in the present case (0.20 nmol/L). Considering the very low serum potassium level and a state of expanded effective arterial blood volume, serum aldosterone could be expected to be significantly decreased.

The metabolic alkalosis seen in this case was due to a rare cause, the ectopic adrenocorticotropic hormone syndrome (EAS). In conditions of ACTH excess, such as pituitary adenoma or ectopic ACTH production, Cushing's syndrome occurs, along with features of hyperaldosteronism. In our case, worsening hypertension and diabetes, hypokalaemia, metabolic alkalosis and oedema were present. Interestingly, a near-nephrotic range proteinuria appeared. Although a kidney biopsy was not performed, it is very likely that proteinuria in this case was due to tubular overflow. More than 80% of Cushing's syndrome patients present increased albuminuria with normal kidney histology [2]. It has been shown that in patients with hyperaldosteronism secondary to adrenal adenoma, hyperfiltration and albuminuria occurs [3]. In addition, hypercortisolism reduces thyroid stimulating hormone secretion. It is interesting to note that in our case, proteinuria disappeared after ketoconazole initiation.

In a series of EAS, Torpy *et al.* [4] described a 78% prevalence for hypertension and 57% for hypokalaemia. Ectopic ACTH syndrome has been associated to several cancer types, such as small-cell lung cancer [4–6], bronchial carcinoid tumours [4], large-cell lung cancer [7], prostate adenocarcinoma and breast cancer, among others.

Ketoconazole is used in the management of EAS by its known effect on inhibition of several enzymes involved in glucocorticoid synthesis [8]. Despite showing a good initial effect [9, 10], there is a high rate of cortisol escape [10], suggesting that the ultimate control of EAS is dependent on the successful treatment of the underlying tumour.

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Conflict of interest statement. None declared.

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