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CLINICAL REPORT

Ectopic ACTH syndrome revealed as severe hypokalemia and persistent hypertension during the perioperative period: a case report

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Abstract Both severe hypokalemia and persistent hypertension are clinical symptoms of hyperaldosteronism. Hyperaldosteronism may occur as a primary or secondary syndrome. Excess ACTH produced ectopically by tumors may induce hyperaldosteronism through the mineralocorticoid activity of glucocorticoids that are upregulated by ACTH. Licorice, with the active ingredient glycyrrhiza, is also a well-known inducer of hyperaldosteronism under specific conditions. In this report, we describe a case of severe hypokalemia caused by ectopic ACTH syndrome (EAS) elicited by an intrathoracic carcinoid tumor, which had transformed to produce ACTH during the 6-year clinical course, and was modulated by licorice ingestion. Hypokalemia was not clearly recognized preoperatively but became obvious within 3 h of general anesthesia with epidural blockade. At the end of anesthesia, arterial blood gas analysis indicated severe hypokalemia ($[K^+] = 1.7$ mEq/l) and metabolic alkalosis (pH 7.56, $PaCO_2 = 54.9$ mmHg, $HCO_3^- = 44.5$ mmol/l, BE = 21.8 mmol/l), without any typical symptoms such as muscle weakness or ECG abnormalities. The hypokalemia was resistant to potassium supplementation and persisted for 4 days. Perioperative imbalance between the administration and elimination of potassium and surgical stress might contribute to the rapid exacerbation and induce the clinical manifestation of EAS.

Keywords Hypokalemia · Ectopic ACTH syndrome · Cushing's syndrome · Licorice · Perioperative period

Introduction

Hypokalemia is one of the most common pathological states observed during the perioperative period. However, moderate and severe hypokalemia with persistent hypertension may be a consequence of more serious conditions, such as hyperaldosteronism or excess mineralocorticoid activity [1, 2]. Diuretics, such as thiazide and loop diuretics, are a common cause of hypokalemia. In addition, pathological states that lead to high mineralocorticoid activity can cause excessive urinary loss of potassium and hypertension. These conditions include tumors of the adrenal glands and ingestion of glycyrrhizin as an extract of licorice. Glucocorticoid excessive states such as Cushing's syndrome (CS) also induce hypokalemia and hypertension. One of the most common causes of adrenocorticotropic hormone (ACTH)-dependent CS or ectopic ACTH syndrome (EAS) is ACTH-producing tumors [3, 4]. In this article, we describe a case of severe hypokalemia or EAS, which was revealed during anesthesia for resection of a recurrent carcinoid tumor, which had transformed to produce ACTH during the 6 years of the clinical course.

Case report

A 64-year-old man with recurrent intrathoracic tumor was admitted for tumor resection. An anterior mediastinal tumor was found during a regular physical checkup and was resected surgically 6 years prior. The tumor was

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diagnosed as a nonsecreting neuroendocrine tumor or atypical carcinoid based on pathological analysis of the surgical specimen. The tumor recurred even after chemotherapy and radiation therapy, 3 years after the surgery. He underwent a second operation for surgical resection. Two years later, metastasis and dissemination of the tumor was identified again after chemotherapy and radiation therapy.

The patient was 171.3 cm tall and weighed 70.1 kg. Blood pressure was 162/85 mmHg and heart rate (HR) was 75 bpm at the time of admission. He claimed that he had experienced whole-body weakness, but other abnormal physical findings, such as central obesity, skin pigmentation, and pitting edema, were not observed. He was prescribed the Ca^{2+} channel blocker amlodipine, the β-blocker carbedirol, and some Chinese herbal medicines. The laboratory data at 2 weeks before the operation are presented in Table 1.

Preoperative blood pressure (BP) was 150/90 mmHg and HR was 95 bpm in the supine position in the operating room. After placement of the epidural catheter at the T5–T6 intervertebral space, general anesthesia was induced with propofol 50 mg and fentanyl 100 μg. Intubation of the trachea and left bronchus with a double-lumen tube was facilitated with vecuronium. Anesthesia was maintained with 1.25–1.5% sevoflurane in air/oxygen and 0.05–0.3 μg/kg/min remifentanil and epidural administration of fentanyl and ropivacaine. There was considerable difficulty in maintaining a stable BP (Fig. 1). He emerged from anesthesia promptly and was successfully extubated. Estimated blood loss was minimal, and a total of 1,250 ml crystalloid fluid was infused during the 2 h and 37 min of anesthesia. Urine output was 260 ml. Arterial blood gas (ABG) analysis revealed severe hypokalemia with metabolic alkalosis (Table 1). No ECG waveform or neurological abnormalities were observed. The patient did not complain of muscle weakness, hyporeflexia, or tetany. Revision of his medical prescriptions revealed that Chinese herbal medicines (*Bu zhong yi qi tang* and *Shi quan da bu tang*) containing licorice extract, which may induce pseudo-aldosteronism, were on the list. Thus, he was tentatively diagnosed as having pseudo-aldosteronism caused by licorice. Hypokalemia (1.53 mEq/l) persisted at postoperative day (POD) 1, even after the administration of 100 mEq potassium. At that time, his consciousness was clear but he exhibited difficulty in speaking and weakening of grip strength. Paroxysmal atrial contraction and paroxysmal ventricular contractions were recognized sporadically on ECG. He was transferred to the intensive care unit for further observation and treatment. The findings of endocrine and urinalysis examinations are shown in Table 2. Urinary potassium excretion was 95.4 mEq/day at POD 2. These findings prompted us to examine ACTH production in the resected tumors from this operation and the second operation, although ACTH was negative in the specimen from the first surgery. Immunological staining was positive for ACTH. Thus, he was finally diagnosed with CS resulting from ectopic ACTH production, which was exacerbated by licorice. Administration of potassium (250 mEq/day) and spironolactone (100 mg/day) was continued for 2 days ($[K^+] = 2.5$ mEq/l). His ABG data from POD 2 to POD 6 are indicated in Table 1.

At POD 10, he developed psychosis and was diagnosed with steroid-induced psychosis. At POD 13, he developed pneumonia and was diagnosed with *Pneumocystis carinii* pneumonia. Then, he was treated with antibiotics including trimethoprim–sulfamethoxazole. The symptoms disappeared by POD 38. A synthetic somatostatin analogue was also prescribed to treat elevated serum ACTH level.

Table 1 Time-series data of arterial blood gas (ABG) analysis

	Preoperation room air	End of anesthesia O_2 4 l mask	POD 1 O_2 2 l nasal	POD 2 room air	POD 4 room air	POD 6 room air
BP (HR)	155/99 (92)	153/72 (81)	154/93 (77)	156/120 (76)	158/109 (82)	179/122 (88)
Antihypertensive medicine	Carvedilol 20 mg + amlodipine 10 mg/day					
pH	7.481	7.549	7.537	7.506	7.501	7.471
PaO_2 (mmHg)	86.7	136.8	104.6	79.2	73.2	59.3
$PaCO_2$ (mmHg)	39.5	54.9	57.8	52.7	45.2	41.2
BE (mmol/l)	5	21	21.8	15.8	9.9	5.2
HCO_3^- (mmol/l)	28.8	46.9	48	40.7	34.5	29.4
Na^+ (mmol/l)	145	143.1	149.7	143	142	140.9
K^+ (mmol/l)	3.2	1.6	1.53	2.46	2.76	3.39
Cl^- (mmol/l)	103	98	92	92	93	98
Lactate (mg/dl)	1.14	11.8		22	23.1	23.5
Ca^{2+} (mmol/l)	1.14	1.03	0.99	0.96	0.96	1.05

BP blood pressure, *HR* heart rate, *POD* postoperative day

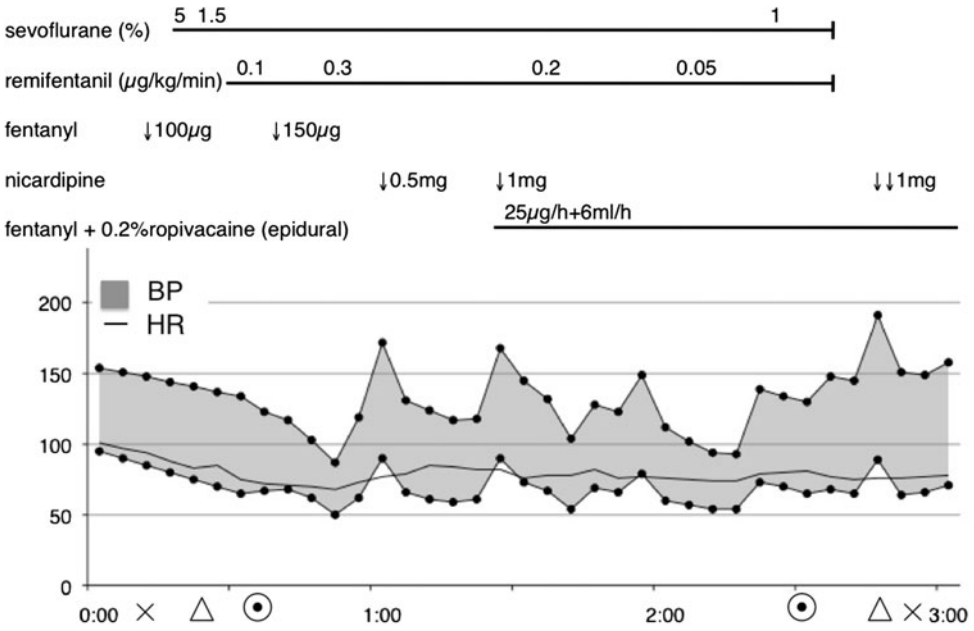

Fig. 1 Physiological parameters during anesthesia showing instability of blood pressure. *BP* blood pressure, *HR* heart rate, *X* start or end of the anesthesia, *triangle* intubation or extubation of the trachea, *double circle* start or end of the operation

Table 2 Hormonal data on POD 1

		Reference range
ACTH (pg/dl)	255	7–56
Cortisol (pg/dl)	66.9	5–15
Aldosterone (pg/dl)	149	30–159
Renin activity (ng/ml/h)	0.2	0.2–2.7
Insulin (μU/ml)	8.1	3–15
hANP (pg/ml)	218	8.0–32.2
hBNP (pg/ml)	340.1	<18.4
TSH (μU/ml)	0.266	0.5–5.0
Free T4 (ng/dl)	1.04	0.88–1.62
Free T3 (ng/dl)	1.45	2.33–4.00
Urine cortisol (μg/day)	4,879	11.2–80.3
Urine 5-HIAA (mg/day)	9.6	1.0–6.0
17-KS (mg/day)	52.4	2.4–11.0
17-OHCS (mg/day)	152.5	2.2–7.3

hANP human atrial natriuretic polypeptide, *hBNP* human brain natriuretic polypeptide, *TSH* thyroid-stimulating hormone, *5-HIAA* 5-hydroxyindoleacetic acid, *17-KS* 17-ketosteroid, *17-OHCS* hydroxycorticosteroid

Eventually, he survived the ectopic ACTH syndrome and was discharged from the hospital without disabilities.

Discussion

EAS represents approximately 10–15% of all types of CS [4, 5]. Neuroendocrine or non-endocrine tumors may be associated with EAS, but the more prevalent tumors are bronchial carcinoids, small cell lung carcinomas, pancreatic carcinoids, thymic carcinoids, medullary carcinomas of the thyroid, and pheochromocytomas [6]. The diagnosis of the EAS is typically suggested by the Cushingoid appearance, marked hypokalemia, and the markedly increased 24-h free cortisol excretion and elevated serum ACTH [5]. However, according to previous reports, the clinical features of EAS are sometimes subtle, and the diagnosis is missed frequently [3, 5]. Indeed, preoperatively, the patient did not manifest any typical symptoms of CS without hypertension.

In this case, the tumor was proven to be a thymic carcinoid that secreted ACTH. Thymic carcinoids are classified as neuroendocrine carcinomas and account for approximately 2–4% of all anterior mediastinal tumors. Thymic carcinoids may be associated with EAS or comprise a proportion of the multiple endocrine neoplasms type 1 syndrome [7–9]. However, ACTH staining on the sample obtained during the first operation was negative. The evidence indicated that the tumor had transformed to produce ACTH during the 6-year-long clinical history. It is well known that thymic carcinoids often secrete one or several hormones. This case supports the potential for a change of the hormonal activity as they grow and relapse [9]. The recurrent carcinoid was not a single tumor, and not all the tumors were resected. Residual tumors might secrete ACTH even after the surgical operation. Figure 2 indicates the hypertrophy of the right adrenal gland at POD 31, which was associated with the persistent high serum ACTH.

Chinese herbal medicines that contain an extract of licorice may induce a syndrome presenting with hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity, and low plasma aldosterone levels [10]. Glycyrrhizin leads to failure of conversion of cortisol to

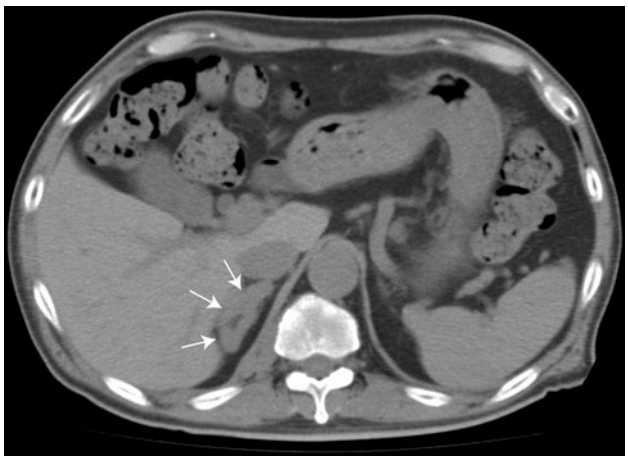

Fig. 2 Abdominal computed tomography (CT) image. *White arrows* indicate hypertrophy of the right adrenal gland, which was assumed to be a consequence of high serum ACTH

cortisone at aldosterone-binding sites, such as the cortical collecting tubules. Consequently, cortisol binds avidly to the mineralocorticoid receptor in the kidneys, resulting in hypertension, metabolic alkalosis, and excessive urinary loss of potassium [11]. Because we found licorice-containing herbal drugs in his prescription list, and pseudo-aldosteronism is usually associated with hypokalemia and hypertension, we tentatively diagnosed the patient with licorice-induced pseudo-aldosteronism. The total licorice dose was 1.75 g/day, which contained glycyrrhizin more than 44 mg/day for 4 months. Although 44 mg/day of glycyrrhizin intake may not be enough to induce the pseudo-aldosteronism, there are several reports of pseudo-aldosteronism induced by the usual dose or even low-dose intake of glycyrrhizin [12]. Moreover, information that the tumor obtained during the initial resection was hormonally inactive might be misleading.

At POD 2, the laboratory data revealed elevated serum ACTH and cortisol with normal renin activity and plasma aldosterone, leading us to the final diagnosis, which was confirmed by the pathological analysis of the specimen excised from the most recent operation. The symptoms of hypokalemia, which were not present during the preoperative period, were explicit during the operation. Fasting for more than 9 h and loading of less than 5 mEq potassium during anesthesia did not match the urinary potassium loss. In addition, activation of the hypothalamic–pituitary axis of the neuroendocrine system by surgical stress, with perioperative psychological stress, might trigger the sequential pathological processes in this case.

In summary, we described a case of severe hypokalemia resulting from ectopic EAS elicited by an intrathoracic carcinoid tumor, which had transformed to produce ACTH during the 6-year clinical course and was modulated by licorice ingestion.

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