中文題目：以嚴重低血鉀與代謝性鹼血症表現之肺小細胞癌及其所致之異源性腎上腺皮質醇症候群

英文題目：Severe hypokalemia and metabolic alkalosis as the presentation of ectopic adrenocorticotropic hormone (ACTH) syndrome from small cell lung cancer

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Abstract:

Cushing's syndrome is a consequence of excessive glucocorticoid. It is difficult to diagnose because its clinical manifestations vary significantly. Ectopic adrenocorticotropic hormone (ACTH) syndrome accounts for around 15% of cases of Cushing's syndrome. Importantly, there is often an underlying malignancy hidden beneath ectopic ACTH syndrome. Timely diagnosis is associated with the prognosis of patients. We present a case of a 65-year-old man who was diagnosed with ectopic ACTH syndrome resulting from small cell lung cancer.

Case presentation:

A 65-year-old man has hypertension and diabetes mellitus without control for years. He had been in his usual state of health until 3 weeks prior to this admission. He presented with generally edema over 4 limbs for about 3 weeks. The edema progressively worsened so he visited outpatient clinics for help. On physical examinations, some papules were noted over the forehead and four limb edema were also found. Laboratory data showed severe hypokalemia with serum potassium level of 1.6 mmol/L. He was further referred to the emergency department and was admitted for severe hypokalemia. At admission, the blood pressure was 142/87mmHg. The laboratory data were significant for arterial blood pH of 7.564 and bicarbonate of 33.4 mmol/L, consistent with metabolic alkalosis. The transtubular potassium gradient (TTKG) was 5.02. The ratio of urinary potassium to creatinine was 13.08 mEq/g initially, which was increased to 53.6 mEq/g after a repeated test. The serum cortisol level was 59.41 μg/dL and serum adrenocorticotropic hormone (ACTH) was 865 pg/ml, respectively. The abdominal ultrasound revealed a right adrenal hypoechoic nodule about 4.9cm.

Under the clinical suspicion of Cushing's syndrome, we arranged an overnight

dexamethasone suppression test. The cortisol level was not suppressible at 49.41 μg/dL. For further confirmation, we performed a low dose dexamethasone suppression test. The serum cortisol level was still not suppressible. In addition, the significantly elevated ACTH level implied the diagnosis of ACTH-dependent Cushing's syndrome. For further differential diagnosis, we arranged magnetic resonance imaging of the head, which revealed no visible pituitary tumor. However, possible bone metastasis in the right mastoid region was accidentally found. Computed tomography of the chest was performed and showed bilateral lung metastasis with multiple lymphadenopathies at right hilar, mediastinal and right supraclavicular region. Bilateral adrenal hyperplasia was also found in this study.

The patient underwent bronchoscope and endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal lymph nodes. The pathology of the lymph node biopsy revealed small cell lung cancer (SCLC). Meanwhile, the results of high dose dexamethasone suppression test confirmed ectopic ACTH syndrome.

We had prescribed aggressive potassium supplement via intravenous and oral route though with limited success. The patient underwent his first cycle of chemotherapy with etoposide 150mg and cisplatin 150 mg for the small cell lung cancer without delay. After chemotherapy and potassium supplement with spironolactone, he was discharged. However, he visited the emergency department on the 9th day after his discharge from the first chemotherapy treatment. He presented with general malaise, anorexia and watery diarrhea. Severe hypokalemia persisted. Febrile neutropenia was diagnosed and intravenous cefepime was administered. However, his condition rapidly deteriorated with persistent fever, shock, hypoxemia and consciousness disturbance even under the support of intravenous fluid challenge and norepinephrine infusion. His family eventually decided to have palliative management for the patient and the patient expired on the second day of the emergency department. The septic work up afterwards revealed *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* bacteremia.

Discussion:

The clinical presentations of severe hypokalemia, metabolic alkalosis, and increased renal potassium loss imply increased distal tubular potassium excretion. The presence of edema, high blood pressure, and hypokalemia refractory to medical

treatment in this patient further suggests hypercortisolism or mineralocorticoid excess, either primary or secondary.

The presence of excess serum cortisol overwhelms the ability of 11-β-hydroxysteroid dehydrogenase to convert cortisol to cortisone. Compared with cortisone, cortisol has a significantly higher affinity to and causes activation of the epithelial sodium channel (ENaC) in the distal renal tubules, resulting in increased distal sodium reabsorption, a negative transluminal electric gradient, and increased potassium and proton secretion.

Cushing's syndrome manifests with symptoms and signs of glucocorticoid excess. Clinical manifestations vary according to the chronicity of exposure to glucocorticoid and the amount of glucocorticoid produced. Glucocorticoids participate in the metabolism and homeostasis involving multiple organs and systems, thus patients with Cushing's syndrome could have remarkable morbidity and even mortality.

After exclusion of iatrogenic causes, Cushing's syndrome could be classified as ACTH-dependent or ACTH-independent. In ACTH-dependent Cushing's syndrome, we may further differentiate by high dose dexamethasone suppression test, advanced image studies such as MRI of the head or inferior petrosal sinus sampling. Ectopic ACTH syndrome usually has worse outcomes compared to other Cushing's syndrome because of potential underlying malignancy. The treatment of ectopic ACTH syndrome mainly stems from dealing with source control including surgical excision and/or cytotoxic therapy. In addition to electrolyte imbalance, edema, and high blood pressure, the excess glucocorticoid also has a negative impact on immune function. Control of the excess cortisol burden before cancer treatment with adrenal enzyme inhibitors such as ketoconazole or metyrapone may be beneficial to reduce the risk of infection in these patients.