Intractable Hypokalemia: a Red Herring for Rapidly Evolving Ectopic Cushing's Syndrome

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Cushing's syndrome is a rare disorder resulting from prolonged exposure to excess glucocorticoids. The syndrome is known for its highly variable clinical presentation, which may include weight gain with central obesity, new and frequently uncontrolled diabetes mellitus, hypertension, osteoporosis, muscle weakness, hirsutism, skin thinning, decrease in libido, and infertility. Chronic exogenous corticosteroid use is the most common cause. The most common etiologies of endogenous Cushing's syndrome are a pituitary adrenocorticotropic hormone (ACTH)-secreting adenoma (Cushing's disease) in 60–70% of patients and primary adrenal Cushing's syndrome in 20–25%. The remaining 5–10% of cases represent the ectopic Cushing's syndrome and are the result of paraneoplastic ectopic ACTH and corticotropin-releasing hormone (CRH) secretion. The most prevalent tumors associated with ectopic Cushing's syndrome are small cell carcinoma of the lung (SCLC), pulmonary carcinoid tumor, pancreatic neuroendocrine tumors (PNETs), thymic NETs, gastrinomas, medullary thyroid cancer, and pheochromocytoma. These cases are characterized by a particular clinical presentation, dominated by muscle wasting and electrolyte imbalances, and are associated with a poor prognosis [1].

We report on a patient with an unusually rapid evolvement of hypokalemia, hypertension, and edema while hospitalized for evaluation of metastatic disease of unknown origin.

PATIENT DESCRIPTION

A 69 year old retired police officer presented to the emergency department with right upper quadrant abdominal pain. Apart from 50 pack-years of smoking and essential hypertension medically controlled with an angiotensin-converting-enzyme inhibitor (2.5 mg ramipril) and an alpha-blocker (doxazosin mesylate 4 mg), he underwent partial nephrectomy 13 years prior to his current admission due to localized clear cell renal carcinoma. Vital signs were in the normal range, and no significant findings were noted on physical examination. Abdominal ultrasonography showed a gallbladder with a moderate amount of gallstones and a hepatic hypoechoic lesion measuring 6 × 9 mm. His pain lessened while in the emergency department and he was discharged with a presumed diagnosis of biliary colic. Further ambulatory evaluation of the hepatic lesion was advised.

Two weeks later, the patient returned to the emergency department with a peculiar set of complaints. The abdominal pain reappeared 4 days before his admission, gradually worsening and radiating to his right leg. In addition, a non-specific chest pain emerged. The patient mentioned that deep inhalation eased the pain. No recent weight loss, fatigue, or loss of appetite were reported. The only abnormal findings on the physical exam were abdominal right upper quadrant tenderness with no peritoneal signs and mild pitting edema in his legs.

Laboratory results showed that all electrolyte levels were within the normal range, and gamma glutamyl transpeptidase and lactate dehydrogenase levels were slightly elevated. Electrocardiogram and cardiac enzymes were also unexceptional. A thoracic and abdominal non-contrast computed tomography scan was performed, which demonstrated an enlarged calcified hilar lymph node, a soft tissue mass adjacent to the second rib, and multiple hypodense liver lesions, the largest measuring 16 mm in width, which is consistent with liver metastases [Figure 1A]. An ultrasound-guided biopsy of the liver lesions was performed, and the patient was discharged for further ambulatory evaluation.

A week and a half later, he was readmitted with dyspnea, orthopnea, mild room air hypoxemia, and polyuria, as well as uncontrolled elevated blood pressure up to 195/95 mmHg and worsening peripheral pitting edema. An echocardiographic study performed during his stay ruled out systolic dysfunction.

Throughout the current hospitalization, the patient experienced recurrent bouts of hypertension with systolic blood pressure reaching 190 mmHg, new onset metabolic alkalosis, and hypokalemia (range 2.7–3.1 mmol/L) that was refractory to continuous intravenous potassium supplementation. The biopsy from the hepatic lesion was consistent with metastatic, aggressive, and

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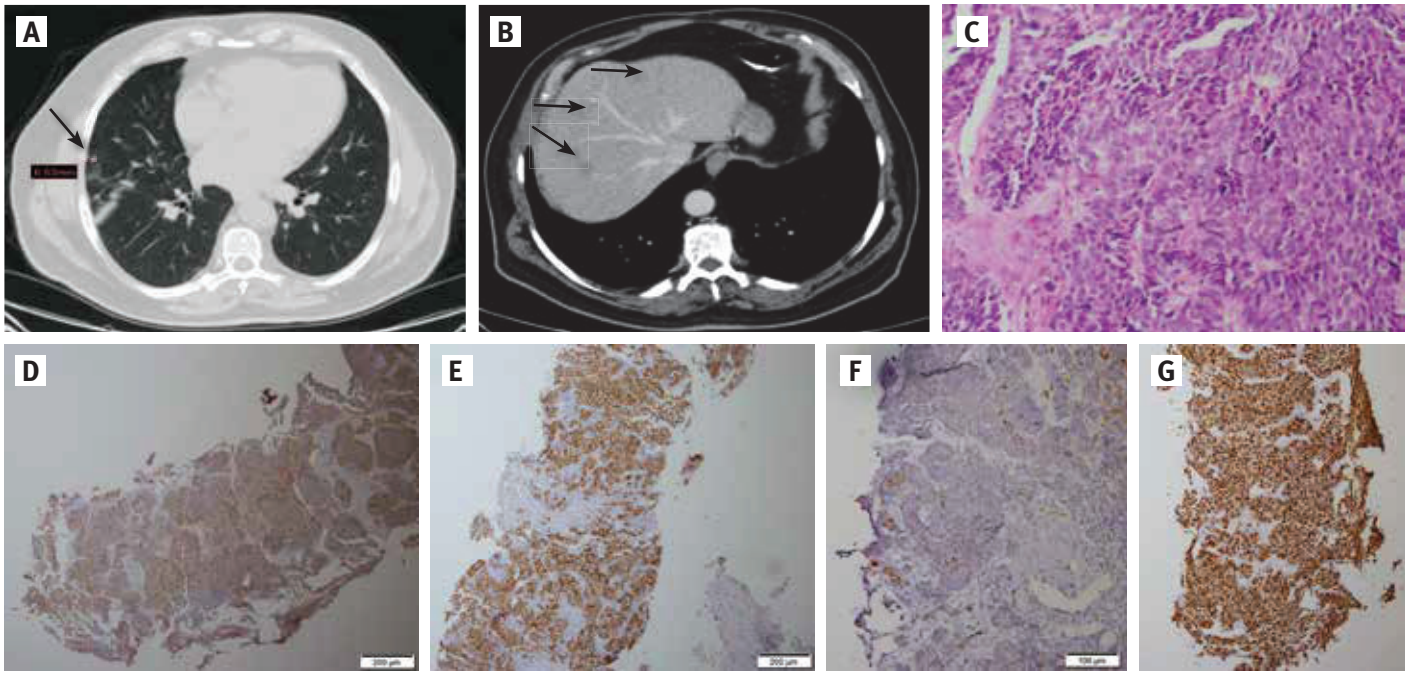
Figure 1. Results from a thoracic and abdominal non-contrast computed tomography (CT) scan. [A] Suspected nodule measuring 6.5 mm in the right lung (arrow). **[B]** Abdominal CT performed during the second admission to the emergency room showing multiple liver metastases (arrows).
Histology slides from the hepatic mass biopsy. [C] Hematoxylin and eosin stain (×400 magnification) showing small cell carcinoma cells invading the hepatic tissue. **[D]** Chromogranin immunostain (×100 magnification) showing tumor cells highlighted by the neuroendocrine marker chromogranin in brown. **[E]** TTF1 immunostain (×100 magnification) showing tumor cells positive for TTF-1 in brown, suggesting probable pulmonary origin. **[F]** Ki-67 proliferation index was ‹ 60%, implying the aggressive nature of the tumor. **[G]** ACTH immunostain (×200 magnification) arrows point to clusters of positively stained tumor cells indicating that ACTH is secreted by these cells



ACTH = adrenocorticotropic hormone, TTF1 = thyroid transcription factor 1

poorly differentiated SCLC. The tumor cells stained positive for chromogranin, thyroid transcription factor 1, and focally for synaptophysin, with a MIB-1 (Ki67) proliferation index higher than 60% [Figure 1C–G].

The rapid clinical deterioration, exacerbation of arterial hypertension, hypokalemic-alkalosis, and the peripheral edema in the context of a tumor raised the possibility of a paraneoplastic effect. Further endocrine workup revealed highly elevated levels of ACTH (81 pmol/L; normal range 1.9–10.2 pmol/L) and cortisol levels of 3343 nmol/L. The diagnosis of Cushing's syndrome mediated by ectopic ACTH secretion from the tumor cells was confirmed by the demonstration of ACTH in tumor cells by immunochemistry. The patient was transferred to the oncology department and started treatment with cisplatin. He tolerated the first treatment and was discharged for further home care. At the 2 week follow-up, the patient's electrolyte disturbances had resolved without additional specific treatment.

COMMENT

Lung cancer, and especially SCLC, are known for causing a variety of paraneoplastic phenomena. The endocrine paraneoplastic syndrome most frequently associated with SCLC is the inappropriate antidiuretic hormone syndrome (SIADH), which can be detected in up to 16% of SCLC patients. The second most common diagnosis is ectopic ACTH-mediated Cushing's syndrome [1]. Ectopic ACTH-mediated Cushing's syndrome is associated with a distinct set of symptoms that typically develop early in the course of the disease. These symptoms, predominantly edema, hypertension, and electrolyte imbalances, precede classical physical findings associated with Cushing's disease [2] but the more prevalent tumors are bronchial carcinoids, small cell lung carcinomas, pancreatic carcinoids, thymic carcinoids, medullary carcinomas of the thyroid, and pheochromocytomas. Occult tumors are highly represented in all the series (12–38%). In a retrospective review of 23 cases diagnosed with SCLC and Cushing's syndrome with ectopic ACTH production, the most frequent physical findings included edema (83%) and proximal myopathy (61%). Furthermore, all but one case included hypokalemic alkalosis [3]. In recent reviews and case reports, hypertension and hyperglycemia were also included as common presenting symptoms [4].

While several case reports have previously described Cushing's syndrome as the presentation of subsequently diagnosed

SCLC, the time frame of sign and symptom onset was not documented objectively. The current case enabled a unique opportunity to describe the dynamics of the onset of ectopic ACTH-dependent syndrome. The documented rapid transition from asymptomatic to grossly apparent Cushing's syndrome in less than 1 month underscores the importance of close follow-up of patients with SCLC and a low threshold of suspicion for this phenomenon.

Early recognition should enable timely therapy to avoid complications of prolonged hypercortisolism, such as infection, cardiac failure, thromboembolism, and death [2]. The central therapy is directed toward lowering the tumor burden. Moreover, it has been shown that hypokalemia and hypertension may be treated with spironolactone [5]. Clinical judgment is necessary to determine the treatment plan for direct inhibition of cortisol secretion according to the severity of hypercortisolemia and the safety of the agents. A variety of different agents are available with ketoconazole and have been reported as being very effective [4].

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Capsule

Treating stroke with a microRNA mimic

The loss and subsequent return of blood flow in the brain that occurs with a stroke damages brain tissue and can be lethal or severely impair cognitive and motor functions. **Kim** et al. treated rodents with an oligonucleotide mimicking the microRNA miR-7 either before or within 30 minutes of an experimentally induced stroke. The approach successfully reduced the amount of brain damage and improved motor recovery in the animals. The mimic appeared to work by repressing the expression of the protein α-synuclein, which is associated with neuronal death in various diseases.

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Eitan Israeli

Capsule

2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis

In the January 2019 issue of *Arthritis Care and Research*, **Singh** et al. described evidence-based guidelines for the pharmacologic and non-pharmacologic treatment of psoriatic arthritis (PsA), as a collaboration between the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF). They identified critical outcomes in PsA and clinically relevant PICO (population/ intervention/ comparator/outcomes) questions. A literature review team performed a systematic literature review to summarize evidence supporting the benefits and harms of available pharmacologic and non-pharmacologic therapies for PsA. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to rate the quality of the evidence. A voting panel, including rheumatologists, dermatologists, other health professionals, and patients, achieved consensus on the direction and the strength of the recommendations. The guidelines cover the management of active PsA in patients who are treatment-naïve and those who continue to have active PsA despite treatment and addresses the use of oral small molecules, tumor necrosis factor inhibitors, interleukin-12/23 inhibitors (IL-12/23i), IL-17 inhibitors, CTLA4-Ig (abatacept), and a JAK inhibitor (tofacitinib). The authors also developed recommendations for psoriatic spondylitis, predominant enthesitis, and treatment in the presence of concomitant inflammatory bowel disease, diabetes, or serious infections. They formulated recommendations for a treat-to-target strategy, vaccinations, and non-pharmacologic therapies. Six percent of the recommendations were strong and 94% conditional, indicating the importance of active discussion between the healthcare provider and the patient to choose the optimal treatment.

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Eitan Israeli

"Nurture your minds with great thoughts. To believe in the heroic makes heroes"

Benjamin Disraeli (1804–1881), British Prime Minister