CLINICAL VIGNETTE

Ectopic Cushing's Syndrome in a Patient with Metastatic Neuroendocrine Tumor

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Case

A 51-year-old male with a history of neuroendocrine tumor (NET) of unknown origin, metastatic to lymph nodes, bone, and pericardium, on monthly lanreotide, presented with progressively worsening fatigue, lower extremity swelling, and intermittent confusion. He had been hospitalized twice in the prior month for hypokalemia without a clearly determined etiology, and was started on spironolactone for the edema and potassium supplementation for hypokalemia.

Physical examination was remarkable for 3+ pitting edema in the bilateral lower extremities to the mid-shin, as well as supraclavicular and cervical lymphadenopathy. Neurologic and pulmonary exams were normal. Admission laboratory studies were notable for potassium 3.0 mmol/L, glucose 300 mg/dL, TSH 0.54 mIU/L, free T4 0.4 ng/dL, and total T3 30 ng/dL. Additional tests included a 24-hour urine free cortisol of 30,132 µg/day (upper limit of normal [ULN] 60 µg/day), ACTH level of 1109 pg/mL (ULN 59 pg/mL), 8am serum cortisol of 156 mcg/dL, plasma renin activity < 0.1 ng/mL/hr, and aldosterone level 4 ng/dL. Pituitary MRI was negative and high-dose dexamethasone suppression test confirmed ectopic Cushing's syndrome. Due to the suspicion of ectopic ACTH secretion by his widely metastatic NET, endocrine surgery was consulted, and bilateral adrenalectomy was scheduled.

In the days prior to surgery, the patient's clinical status rapidly deteriorated. On hospital day 3, he developed pleuritic chest pain and hemoptysis. Chest x-ray demonstrated multiple nodular mass-like opacities concerning for multifocal pneumonia. CT chest revealed multiple coalescent dense airspace consolidations bilaterally, which were subsequently found to be secondary to invasive pulmonary aspergillosis on sputum culture. Infectious disease was consulted and started empiric broad-spectrum antibiotics and voriconazole.

On hospital day 7, he developed acute left-sided weakness and aphasia concerning for stroke. MRI stroke protocol showed bilateral infarcts in addition to a new left MCA aneurysm. The precise etiology of his stroke was not determined, though it was presumed due to hypercoagulable state related to Cushing's syndrome. Septic emboli were excluded given negative blood cultures, normal LP, TEE without vegetation, and cardiac MRI demonstrating no intracardiac mass. Nevertheless, he was determined to be high-risk for venous thromboembolism (VTE) chemoprophylaxis, and retrievable IVC filter was placed to mitigate the risk of perioperative pulmonary embolism.

On hospital day 10, he underwent bilateral adrenalectomy and tolerated the surgery well. He spent an additional two weeks in the surgical ICU, during which he was stabilized on hydrocortisone, fludrocortisone, and levothyroxine. He was discharged with prolonged voriconazole therapy for aspergillus, and with plan to follow-up with oncology for further treatment of his NET.

Discussion

The use of a stepwise diagnostic algorithm in patients with hypercortisolism is necessary to determine the etiology and subsequent appropriate management. The initial step is to confirm hypercortisolism by either two late-night salivary cortisol measurements, two 24-hour urine free cortisol excretion measurements, or overnight 1 mg dexamethasone suppression test. Any abnormal result on initial screening is followed by measurement of the ACTH level to determine if the elevated cortisol is dependent upon ACTH. If the hypercortisolism is ACTH-dependent, high-dose dexamethasone testing, MRI pituitary, and inferior petrosal sinus sampling can be used to determine whether the ACTH secreting entity lies within the pituitary gland Cushing's disease (CD), or from an ectopic source, ectopic Cushing's syndrome (ECS).

Compared to CD, ECS has a higher potential for extreme hypercortisolism.[1] Patients with extreme hypercortisolism are at higher risk for a myriad of systemic complications, including neuropsychiatric disturbances, cardiovascular complications, metabolic derangements, infection, and thrombotic events (TE).[2] Thus, once the diagnosis of ECS has been established, rapid multidisciplinary coordination between endocrinology, oncology, and surgery should mitigate these complications, with definitive treatment occurring within 24-72 hours if life-threatening complications are present. Treatment may include steroidogenesis inhibitors such as ketoconazole or metyrapone, surgical resection of the tumor, and/or bilateral adrenalectomy, in addition to close monitoring for complications related to a patient's cortisol-dependent comorbidities.[3]

Thrombotic events are responsible for a significant proportion of the mortality associated with ECS, with pulmonary embolism accounting for 11%, ischemic cardiac disease for 19%, and stroke for 17% of deaths.[4] Rates of VTE are up to four times greater in ECS than in the general population.[5] Hypercortisolism induces a hypercoagulable state by enhanced

thrombin generation thought due to increased procoagulant factor production (notably, factors VIII, XI, and von Willebrand factor) and impaired fibrinolysis. Additionally, obesity and the postoperative state, risk factors inherent within many patients with ECS independently contribute to the prothrombotic condition.[4] The increased risk of coagulopathy is highest in the first four weeks postoperatively, though the increased risk of TE can last up to one year following surgical cure.[6] Prophylactic anticoagulation is recommended for all ECS patients without a contraindication, especially postoperatively following adrenalectomy, however, no formal guidelines exist for the type or duration of thromboprophylaxis.

Extreme hypercortisolism also impairs immune function via impaired neutrophil activity and down-regulation of proinflammatory cytokines, predisposing patients to severe infections by bacterial and opportunistic pathogens, particularly fungal infections.[7] The anti-inflammatory properties of cortisol may also contribute initially to subclinical manifestations of these infections and contributes to an immune rebound phenomenon after cure that can exacerbate preexisting autoimmune disease.[2] Approximately half of patients presenting with ECS have an associated infection at the time of diagnosis, and thus in addition to directed antimicrobial therapy, lowering of cortisol levels to physiologic ranges is needed to minimize the risk of infectious complications.[8]

Lastly, ECS can lead to a myriad of metabolic and endocrine disturbances, among them hypokalemia and hypothyroidism. Excess mineralocorticoid activity due to increased secretion and decreased inactivation of cortisol and corticosterone induces sodium retention and hypokalemic metabolic alkalosis in the setting of low plasma aldosterone and renin activity, as was observed in our patient.[9] Central hypothyroidism may also develop in patients with ACTH-dependent ECS due to the inhibitory action of endogenous hypercortisolemia on the hypothalamic-pituitary-thyroid axis. This leads to reduction in the release of TRH from the hypothalamus and decrease in the conversion of T4 to T3 peripherally. Serum levels of TSH, T3, FT3, and T4 immediately increase following surgical cure of ECS, and in the majority of patients returned to normal within one-year post-operatively.[10] It is recommended that thyroid hormone replacement therapy be withheld until after surgery to prevent the development of iatrogenic hyperthyroidism.

This case demonstrates the importance of early recognition, rapid diagnosis, and prompt treatment of ACTH-dependent ECS in order to avoid both short and long-term morbidity and mortality associated with this condition.

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