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CLINICAL VIGNETTE

Ectopic Cushing's Syndrome – A Rare Paraneoplastic Manifestation of Metastatic Neuroendocrine Small Cell Bladder Cancer

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Case

A 65-year-old male recently diagnosed with diabetes, hypertension and metastatic bladder/prostate tumor, presented to the hospital with bacteremia after his first chemotherapy session.

The patient was diagnosed with cancer one month prior after developing hematuria. Imaging revealed a 4 cm mass infiltrating his bladder and prostate. He underwent transurethral bladder resection with pathology showing high grade (3/3) neuroendocrine carcinoma. PET/CT showed probable metastases to the liver, bones, and lymph nodes. He started chemotherapy with carboplantin and ectoposide and developed pancytopenia and bacteremia.

On admission, the patient was noted to have hypokalemia of 2.6 mmol/dL with acute kidney injury and eGFR 33 mL/min/1.73 m^2 (his pre-chemotherapy eGFR > 60 mL/min/1.73 $m^{2)}$. Random cortisol level was checked to evaluate hypokalemia and metabolic acidosis. Serum cortisol was markedly elevated at > 63 ug/dL with ACTH elevated at 308 pg/dL. This suggested severe hypercortisolism and the endocrine service was consulted.

Patient reported a one-month history of new symptoms including 20 lbs weight loss, muscle weakness, skin discoloration and thinning, easy bruising, lower extremity swelling, and the development of loose teeth. He denied a prior history of hyperglycemia or hypertension before his recent cancer diagnosis.

On exam, he was comfortable, without fever. Blood pressure was 151/97 with HR 70. He had normal cardiac rate and rhythm with clear lungs. He had 3+ pitting edema in bilateral lower extremity which extended to the scrotum and lower torso. Additionally, he had 4/5 strength in bilateral lower extremities. He did not have purple striae or dorso-cervical fat pad.

Patient underwent a high dose (8mg) dexamethasone suppression test in the hospital, which showed non-suppressed serum cortisol and ACTH, suggesting ectopic Cushing's syndrome (see Table 1). Twenty-four hour urine cortisol test was completed for confirmation and showed a cortisol level more than 10 fold higher than the upper limit of normal. This established the diagnosis of ectopic ACTH mediated Cushing's syndrome. He was started on ketoconazole 200 mg twice a day for his hypercortisolism, along with aggressive potassium supplementation. With initiation of ketoconazole, which was titrated up to 400 mg three times a day, his serum cortisol improved to <20 ug/dL within a few days and his potassium supplement requirement decreased. His lower extremity edema also improved with the addition of IV furosemide. Glucose level also improved with reduced insulin replacement.

Unfortunately, the patient developed bilateral pneumonia, septic shock and multi-organ failure leading to death.

Table 1. Laboratory testing results from hospitalization

Date	3-Mar	5-Mar	10-Mar	17-Mar
Potassium (mmol/L) [ref 3.3-4.8]	2.6	2.9	3.3	5.4
Sodium (mmo/L) [ref 136-145]	142	146	142	139
eGFR (mL/min/1.73m2) [ref >60]	31	33	59	20
Cortisol (ug/dL) [ref 5-21]	>63	59.6 *	19.8	21
ACTH (pg/mL) [ref 7.2-63.3]	308	237*		7.1
24-hour urine cortisol (ug/24 hour) [ref 5-64]		792		
Aldosterone (ng/dL) [ref 0-30]	<1.0			
renin activity (ng/mL/hr) [ref 0.167-5.38]	0.932			

*lab collected 8AM after 8 mg dexamethasone suppression test

Discussion

Ectopic Cushing's syndrome (ECS) is a rare condition accounting for 10-20% of all cases of ACTH-dependent Cushing's

syndrome. While older studies suggested that small cell lung cancer is one of the more common causes of ECS, more recent studies report ECS is more commonly seen in other neuroendocrine tumors (NETs). These include mainly bronchial carcinoids (40% of cases), followed by occult primary (22% of cases) and pancreatic NET (15% of cases).[1] Primary small cell carcinoma of the bladder neuroendocrine tumor may mimic some pathophysiology of small cell lung cancer but is very rare, comprising only less than 1% of all bladder cancers. ECS associated with neuroendocrine tumor of bladder is even more rare. There was only one case of ECS noted to be associated with primary small cell carcinoma of bladder in review of over 8000 cases of primary bladder malignancy in a 28-year retrospective study.[2]

When evaluating rare diseases, having clinical suspicion of disease is crucial. While we typically think of central obesity associated with moon faces and purple striae as specific signs of Cushing's syndrome, rapid progression of tumor growth may result in absence of moon faces and central obesity, due to speed of onset and severity of hypercortisolism.[3] Our patient presented with new onset hypertension, hypokalemia, hyperglycemia, weight loss, muscle weakness and lower extremity edema without central obesity, moon facies or abdominal striae.

Hypertension and hypokalemia are more prevalent presenting symptoms in ECS patients compared to other causes of Cushing's syndrome.[4] ECS patients have more severe hypercortisolism, with significantly higher serum cortisol, ACTH and urine cortisol level compared to other causes of Cushing's syndrome.[5] This elevated level of cortisol is what often leads to more severe hypokalemia[4,6] along with other serious complications that greatly affect survival.[1] Severe infection is a common complication of ECS, with studies suggesting a 23-57% prevalence,[5,6] as well as venous thromboembolism with 14% prevalence.[7] Patients with metastatic cancer are often started on cytotoxic chemotherapy which further increases risk of severe infection and metabolic disturbance, leading to increased morbidity and mortality in patients with hypercortisolism.

It is important that patients with ECS start treatment with adrenolytics as soon as preliminary dynamic tests are completed. In our patient, because the 24-hour urine test can take up to 5-7 days to result, he was started on ketoconazole soon after the 8 mg dexamethasone test was performed to avoid any delay. One or more adrenolytics (ketoconazole, mytyrapone) may be needed to adequately treat hypercortisolism. Somatostatin agonists can also provide improvement as ACTH producing tumors can express these receptors.[8] Starting adrenolytics is recommended prior to curative treatment (surgery or chemotherapy) as it will lower risk of opportunistic infection. Patients undergoing cytotoxic chemotherapy may require titration of adrenolytics, with possible addition of steroid replacement to avoid adrenal insufficiency as well as close metabolic panel monitoring.

When possible, surgery is the recommended treatment of ECS, especially for non-metastatic disease, as surgery may achieve cure in more than 40% of patients.[8] For refractory cases where hypercortisolism is not controlled after medical or surgical treatment, bilateral adrenalectomy should be considered. It has been shown to improve patient outcome at least in the first 2 years after surgery.[1]

While rare, ECS should be suspected in patients with neuroendocrine tumors that develop unexplained new muscle weakness, hypertension, hyperglycemia and hypokalemia. The lack of many typical features of hypercortisolism such as weight gain, moon faces and dorsocervical fat pad does not exclude the diagnosis. Once the diagnosis of ECS is suspected, rapid initiation of treatment of hypercortisolism is important as untreated hypercortisolism has significant morbidity and mortality.

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