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# Ectopic Cushing Syndrome Secondary to Metastatic Small Cell Carcinoma of Unknown Primary: A Multidisciplinary Approach

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## Abstract

*Background*: Small cell lung cancer (SCLC) is a neuroendocrine tumor with the possibility to produce various peptides or hormones that can lead to paraneoplastic syndromes, such as ectopic ACTH secretion (EAS). The diagnosis of EAS is challenging and requires a multidisciplinary approach. *Case Report*: We report a case of a 64-year-old man who presented severe hypokalemia, metabolic alkalosis, worsening hyperglycemia and hypertension, found to have EAS secondary to metastatic small cell carcinoma of unknown primary. *Conclusion*: We review therapeutic options, including chemo-immunotherapy as part of the treatment regimen, for EAS.

**Keywords:** Adrenocorticotropic Hormone, Cushing Syndrome, Neuroendocrine Tumors, Small Cell Carcinoma.

## Introduction

Cushing syndrome results from prolonged exposure to supra-therapeutic glucocorticoid levels. Endogenous causes of Cushing syndrome are far less common than exogenous ones. Population-based studies suggest an incidence of endogenous Cushing syndrome of 0.7-2.4 per million population per year. An estimated 80-85% of Cushing syndrome cases are ACTH-dependent, with less than 20% of all cases of Cushing syndrome thought to be secondary to ectopic ACTH secretion (EAS) [1]. We report a case of a 46-year-old man found to have EAS secondary to metastatic small cell carcinoma of unknown primary with detailed description of his presenting history, initial workup, and treatment course.

## Case Report

The patient is a 46-year-old man who presented with a chief complaint of abdominal pain associated with polydipsia, polyuria, severe fatigue, and a 40-pound weight loss. Past medical history was significant for newly diagnosed hyperlipidemia, type 2 diabetes, and chronic venous disease. He had a cholecystectomy in 1993. He was a former heavy drinker but abstained from alcohol for over 5 years. He did not use tobacco or illicit drugs. He had a family history of cancer of unknown type in two cousins and one aunt.

Initial examination revealed thrush, right upper quadrant and epigastric abdominal tenderness, and acanthosis nigricans. There was no obvious buccal or palmar crease hyperpigmentation. He had 2+ pitting edema to the level of the bilateral knee. He was afebrile, tachycardic to the low 100s, and hypertensive to 154/108. He had Class I obesity with a BMI of 33 and increased abdominal waist circumference. He did not have pink or purple striae, facial plethora, or evidence of a dorsocervical fat pad. The remainder of his examination was unremarkable. Initial laboratory studies were notable for a leukocytosis



 

of 20.7 K/UL with a left-shifted granulocytosis and monocytosis, hypokalemia to 3.1 mmol/L, and a metabolic alkalosis with a pH of 7.57. He had an elevated hemoglobin A1c (HbA1c) to 9.2%.

A diagnosis of Cushing syndrome was suspected due to evidence of hypertension and thrush on examination, as well as the combined laboratory data of hyperglycemia, metabolic alkalosis, and hypokalemia. Hypercortisolism was confirmed via a 1 mg dexamethasone suppression test that revealed an AM cortisol of 36.7 µg/dL (<1.8 µg/dL), and a 24-hour urinary free cortisol (UFC) of 4039.9 µg (4 - 50 µg per 24-hour period). Evening ACTH levels were elevated to 267 pg/mL (<20 pg/mL), confirming ACTH-mediated disease. DHEA-S, aldosterone, and catecholamine levels were normal.

CT chest, abdomen and pelvis with contrast imaging revealed innumerable hypodense liver lesions as well as multiple necrotic enlarged lymph node conglomerations (with the largest dimension being 8 cm) adjacent to the portal vein and pancreas, concerning for metastatic disease. There were no pulmonary lesions. An MRI brain was unremarkable. Liver biopsy revealed a high-grade small cell carcinoma with positive staining for synaptophysin, chromogranin, cytokeratin AE1/AE3 and TTF-1, as well as negative staining for CDX2, SATB2 and LCA. We considered the diagnostic role of bilateral inferior petrosal sinus sampling (BIPSS), even in the setting of high-grade small cell carcinoma. However, 12 mg of dexamethasone was administered by the primary team as part of the patient's emergent chemotherapy regimen at 4 pm, and the subsequent AM cortisol remained elevated at 22.3 µg/dL (<1.8 µg/dL). The standard high dose dexamethasone suppression test was no longer feasible due to continued dexamethasone administration as part of initiated chemotherapy regimen. The lack of cortisol suppression with 12 mg of dexamethasone provided clear evidence of the resistance to feedback inhibition noted in non-pituitary tumors and reinforced our suspicion of ACTH-mediated ectopic Cushing syndrome secondary to small cell carcinoma.

Chemotherapy was urgently initiated in the setting of metastatic small cell carcinoma. The patient was started on palliative carboplatin/etoposide/atezolizumab chemo-immunotherapy for a planned duration of 4 cycles to be followed by maintenance atezolizumab monotherapy. Given the highly chemo-sensitive nature of small cell carcinomas [2], we made the decision to closely monitor the cortisol response to chemotherapy and delay potential initiation of specific cortisol reducing or blocking therapies such as ketoconazole, metyrapone, etc. The patient was also started on apixaban for prophylactic anticoagulation and atovaquone for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis given his extreme hyper-cortisolemia [3]. He was discharged from the hospital with plans to continue chemo-immunotherapy as an outpatient. Basal insulin glargine was initiated with the addition of glimepiride upon discharge.

The patient's first follow up visit took place six weeks post-discharge. By this time, he had received two cycles of chemo-immunotherapy. He underwent repeat imaging and biochemical testing which revealed a moderate decrease in tumor burden and a dramatic decrease in both cortisol and ACTH levels (UFC 5.9 g per 24-hour period, random AM serum cortisol 6.2 g/dL, ACTH 18 pg/mL), consistent with biochemical remission due to normalization of UFC. Atovaquone and apixaban were discontinued. His HbA1c decreased to 6.2%, allowing for a de-escalation of his diabetes regimen. An ACTH-stimulation test was performed with an appropriate increase in serum cortisol to 20.3 g/dL (>18 g/dL), thus ruling out adrenal insufficiency.

The patient had a continued response to chemo-immunotherapy with a significant reduction in tumor burden. Unfortunately, approximately



 

five months after initial presentation he began to show unequivocal biochemical evidence of tumor progression in the form of rising carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), and liver function test (LFT) levels. He was classified as having resistant relapse, and transitioned to second-line paclitaxel chemotherapy. He continued to show evidence of progression of his malignancy seven months after initial presentation and was started on temozolomide and olaparib. His hypercortisolemia returned despite this transition to third-line chemotherapy, with 24-hour UFC levels increasing from a nadir of 1.1 g per 24-hour period to 803 g per 24-hour period. Furthermore, his glycemic control worsened, and diabetes medications were intensified. The patient and his family decided to pursue hospice care.

## Discussion

EAS can occur secondary to benign or malignant neuroendocrine tumors. The diagnosis of EAS is complex and involves multiple steps including dynamic biochemical testing, imaging studies, and potentially bilateral inferior petrosal sinus sampling (BIPSS). Each of these tests should be interpreted within the clinical context and pretest probability [4].

EAS secondary to malignant neuroendocrine tumors is generally associated with markedly elevated ACTH and cortisol levels, although there is an overlap with levels seen in Cushing disease. Malignant neuroendocrine EAS is more likely to present with rapid onset weight loss and catabolic features than pituitary related Cushing disease or EAS secondary to benign neuroendocrine tumors [4]. Furthermore, mineralocorticoid effects (e.g., hypokalemia, metabolic alkalosis) and hyperpigmentation are more often present in the setting of EAS aggressive malignancies. In contrast, EAS resulting from benign and low malignant potential neuroendocrine tumors can be indistinguishable from Cushing disease [4].

Bronchial carcinoid and SCLC together make up 44.4% of all cases of EAS. Thus, chest CT is a crucial part of the workup for ACTH-dependent Cushing syndrome in the setting of negative pituitary imaging [5]. In our patient, the historical fact that he never smoked, and the absence of radiographic evidence of a pulmonary source raised clinical suspicion for extrapulmonary small cell carcinoma (EPSCC) [6]. EPSCC is rare (only 5% of all cases of small cell carcinoma) and the gastrointestinal (GI) tract represents the most common source. Gastrointestinal EPSCC malignancies tend to metastasize to the liver and distant lymph nodes [7]. Our patient's imaging demonstrated innumerable liver metastases as well as multiple necrotic enlarged lymph node conglomerations adjacent to the portal vein and pancreas. Pathology cannot reliably differentiate EPSCC from SCLC; TTF-1 positivity, while more common in pulmonary than extra-pulmonary small cell carcinomas, is not specific enough to confirm a pulmonary source [6,8].

We decided to forgo BIPSS as pituitary imaging did not demonstrate a visible lesion (although a negative MRI does not definitively rule out Cushing disease). BIPSS is invasive and needs to be performed by experienced operators, and in this particular case, the pre-test probability of a pituitary source of ACTH was quite low. In addition, resistance to feedback inhibition with high doses of dexamethasone, very high levels of ACTH and cortisol, catabolic features, and rapid onset of mineralocorticoid effects aligned more with EAS from a malignant tumor. The patient's final diagnosis was EAS secondary to small cell carcinoma of unknown primary. Given the aggressive and metastatic nature of our patient's small cell carcinoma, chemo-immunotherapy was urgently initiated and served as the basis of his treatment. Immune checkpoint inhibitors such as atezolizumab have been FDA approved for SCLC. Our patient was treated with chemotherapy and atezolimumab, an anti-PD-L1 antibody



 

that can cause immune-related adverse events. The incidence of hypophysitis with anti-PD-L1 inhibitors is <0.1%, and the incidence of primary adrenal insufficiency is even rarer [9].

Specific medications for cortisol blockade/ reduction such as ketoconazole, metyrapone, etomidate, mitotane, and mifepristone were not administered, and instead cortisol levels were monitored in response to tumor-specific therapy. Six weeks later, after completion of two cycles of chemo-immunotherapy, the tumor burden decreased with an associated dramatic drop in 24-hour UFC levels from >4000 g to 5.9 g per 24-hour period, along with an improvement in glycemic control. As the cortisol levels dropped dramatically to the normal laboratory range with chemo-immunotherapy, the need for specific medication for cortisol blockade/reduction was eliminated. We monitored the 24-hour UFC, random serum cortisol, and random serum ACTH levels every 1-3 months, and performed an ACTH stimulation test when the levels dropped dramatically. The hyper-cortisolemia ultimately recurred, but by this time, he had failed third line cancer therapy, and was transitioned to hospice care.

This case demonstrates that in exceptional cases of tumors that are known to be highly sensitive to chemo-immunotherapy, with a plan for immediate and urgent administration of therapy, specific anti-hypercortisolism therapy can be held until the initial response to therapy is evaluated. However, this should be closely followed with frequent (every 1-3 months) assessment of the cortisol response to therapy, to detect persistent/ recurrent hyper-cortisolemia, as well as detect adrenal insufficiency, which, although rare, can be life-threatening. The florid nature of our patient's presentation, the existing uncertainty surrounding the primary site of his metastatic cancer, and the rare nature of EAS secondary to small cell carcinoma of unknown primary all provide valuable insights into Cushing syndrome.

## Conclusion

Cushing syndrome due to EAS can present with electrolyte disturbances, hypertension, and hyperglycemia and not typical cushingoid symptoms. The diagnosis of EAS is challenging and requires a multidisciplinary approach. In exceptional cases of chemo-immunotherapy sensitive tumors, specific anti-hypercortisolism therapy can be held until initial response to chemotherapy is evaluated.

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