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Case Report

Severe Ectopic Adrenocorticotropic Hormone Syndrome Due to Pulmonary Carcinoid Tumor: A Case Report and Literature Review

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ABSTRACT

Background/Objective: Pulmonary carcinoid tumors are a rare cause of Cushing's syndrome and usually present with an indolent course. Here, we present a case of rapid onset and severe Cushing's syndrome due to a typical pulmonary carcinoid tumor.
Case Report: A 32-year-old woman developed diabetes, hypertension, and weight gain of 50 pounds over 3 months. Laboratory evaluation was significant for elevated cortisol and adrenocorticotropic hormone levels and levels were nonsuppressible on low and high-dose dexamethasone suppression tests. Chest computed tomography revealed a pulmonary nodule and biopsy showed a typical carcinoid tumor. She was treated with steroidogenesis inhibitors with a plan for surgical excision but developed worsening complications of hypercortisolemia. She eventually underwent cryoablation of the tumor, but unfortunately passed away just 6 months after her initial presentation.
Discussion: Cushing's syndrome in typical pulmonary carcinoid tumors is rarely seen and usually presents with mild hypercortisolism similar to Cushing's disease. Severe hypercortisolemia from typical pulmonary carcinoid tumors can represent a more aggressive pathology or metastatic disease. Severe Cushing's syndrome is associated with significant morbidity and mortality and requires rapid tumor localization as surgical resection can be curative.
Conclusion: This case highlights a rare presentation of severe Cushing's syndrome due to a typical pulmonary carcinoid.

Introduction

Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is a rare clinical presentation that accounts for 10% to 20% of all ACTH-dependent causes of Cushing's syndrome.[1,2] The prevalence of EAS is 1% to 5% in small cell lung cancer (SCLC), 3% in patients with thoracic or gastroenteropancreatic carcinoids, and 0.7% in patients with medullary thyroid carcinoma.[3] The manifestations of Cushing's syndrome in EAS are variable depending on the tumor histopathology and degree of cortisol elevation. Symptoms can range from gradual onset of classic signs and symptoms of Cushing's syndrome to rapid onset with severe hypercortisolemia and high morbidity.[1,2,4,5] Generally, aggressive tumors such as SCLC or widely metastatic cancer have rapid onset of EAS with severe symptoms.[2,5] Alternatively, well-differentiated pulmonary carcinoid is classically an indolent tumor with low metastatic potential and has less severe symptoms.[2,5] Uncontrolled hypercortisolism is associated with a five-fold increased mortality in patients without underlying malignancy.[4,5] The therapeutic goal is to normalize cortisol levels and locate and resect the source of ACTH secretion, as this can be curative.[1-3] We present a case of ectopic ACTH-producing typical pulmonary carcinoid tumor with rapid onset of severe clinical symptoms.

Case Report

A 32-year-old female was admitted to our hospital for worsening lower extremity edema and dyspnea. The patient had

Abbreviations: ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; EAS, ectopic ACTH syndrome; NET, neuroendocrine tumor; RFA, radiofrequency ablation; SCLC, small-cell lung carcinoma.

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Table
Results of Endocrinological Laboratory Tests

Variable	Result	Reference range
Adrenocorticotropic hormone, pg/mL	206	10-60
Cortisol, μg/dL	23.4	5-25
24 h urine free-cortisol, μg/d	2796.6	21-85
After low-dose dexamethasone suppression test cortisol, μg/dL	29.9	
After high-dose dexamethasone suppression test cortisol, μg/dL	49.9	
Dehydroepiandrosterone sulfate (DHEA-S), mcg/dL	318	45-270
Chromogranin, ng/mL	240	<311
Gastrin, pg/mL	276	<100
Post-cryoablation morning cortisol, ug/dL	25.6	5-25

recently been diagnosed with Cushing's syndrome after she developed symptoms of 50-pound weight gain, hyperglycemia, and elevated blood pressure over 3 months. Her other symptoms included mood lability, insomnia, hair thinning, hirsutism, acne, and proximal muscle weakness. Initial laboratory evaluation by her outside endocrinologist showed an elevated random serum cortisol and ACTH level and a significantly elevated 24-hour urinary cortisol level of 2796.6 μg/d (Table). Her other medical history included recently diagnosed lower extremity deep vein thrombosis, 7 mm left pulmonary nodule, nodular liver hyperplasia, and hysterectomy for endometriosis.

Physical examination showed a mildly ill-appearing woman in no acute distress. Vital signs were significant for blood pressure of 192/105 mmHg, heart rate of 103 bpm, height of 150 cm, and weight of 110 kg (body mass index 52.4 kg/m2). She had rounded facies, coarse dark facial hair on her chin, dorsocervical fat pad, and wide violaceous striae across her lateral abdomen and axillary region (Fig. 1). She had decreased proximal strength in her upper and lower extremities and 2+ bilateral lower extremity edema.

Laboratory findings were significant for glucose 325 mg/dL (reference range 70-106 mg/dL), potassium 2.5 mmol/L (reference range 3.5-5.3 mmol/L), and HbA1C 6.7% (reference range 4.8% to 5.6%). Morning serum cortisol level was 32.4 ug/dL (reference range 2.5-19.5 ug/dL) with ACTH level 206 pg/mL (reference range 6-50 pg/mL). A low-dose 1 mg overnight dexamethasone suppression test (DST) revealed a morning cortisol of 29.9 ug/dL, followed by a high-dose 8 mg DST with morning cortisol of 49.9 ug/dL (reference range <1.8ug/dL) and ACTH level of 234 pg/mL (Table).

Highlights

- Presentation of severe Cushing's syndrome in typical pulmonary carcinoid tumor.
- Epidemiology of ectopic adrenocorticotropic hormone syndrome in pulmonary carcinoid.
- Evaluation and management of ectopic adrenocorticotropic hormone syndrome.

Clinical Relevance

This vignette describes an unusual case of a typical pulmonary carcinoid tumor presenting with severe and rapid onset Cushing's syndrome. It reviews the clinical presentation of Cushing's syndrome, epidemiology of typical carcinoid tumors, and diagnostic and therapeutic management of ectopic adrenocorticotropic hormone syndrome.

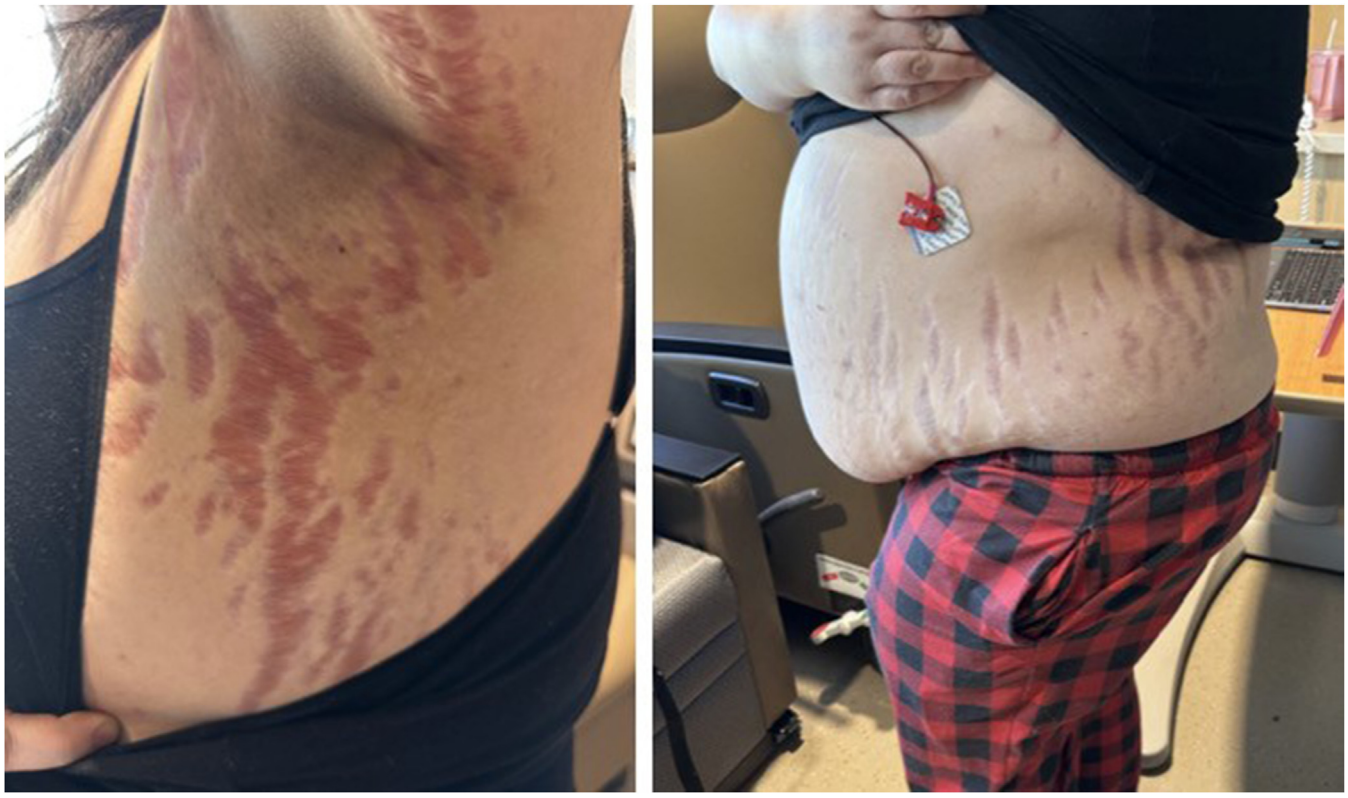

Fig. 1. Photograph of the patient showing violaceous, wide axillary and abdominal striae and central adiposity.

A computed tomography (CT) chest scan showed a noncalcified, well-circumscribed pulmonary nodule in the lingula measuring 1.6 × 1.4 cm without lymphadenopathy. A pituitary magnetic resonance imaging (MRI) showed pituitary stalk thickening without an adenoma.

The clinical symptoms of rapid and severe Cushing's syndrome, failed high-dose DST, and negative pituitary MRI made EAS the most probable diagnosis and the enlarging pulmonary nodule the likely source. Endemic fungal infections, such as coccidiomycosis, were ruled out first. She then underwent an interventional radiology (IR)-guided subcutaneous biopsy of the pulmonary nodule. The pathology returned positive for a neuroendocrine tumor (NET). Histopathology confirmed a typical carcinoid grade 1 tumor. Tumor cell staining was positive for chromogranin and synaptophysin and negative for TTF-1, Napsin A, p40, and CD45. The Ki-67 index was <1%.

The patient had refractory hypokalemia and hypertension requiring potassium supplementation, up to 1200 mg daily, in addition to spironolactone 50 mg twice daily and lisinopril 20 mg once daily. She also had severe hyperglycemia requiring an insulin basal-bolus regimen.

She was discharged home on ketoconazole 200 mg twice daily to control her hypercortisolemia as there were no other treatment options available during her hospitalization at our institution. She then underwent a Dotatate scan for staging and surgical planning, given concern for metastatic disease due to the severity of EAS. The Dotatate scan showed a 1.6 cm × 1.4 cm left pulmonary avid nodule with no avidity in the regional lymph nodes (Fig. 2) and a plan for surgical resection of her single pulmonary nodule was made.

Unfortunately, the patient had multiple complications due to hypercortisolemia requiring recurrent hospitalizations and was unable to undergo her planned surgical resection. The team was also working on obtaining additional medications for her Cushing's while her ketoconazole was being uptitrated. However, no other medications were approved by her insurance, as she exceeded her maximum insurance limit due to her multiple hospitalizations.

One month after her initial evaluation at our institution, she developed peritonitis with diverticular perforation and intra-abdominal abscesses. She also had severe proximal myopathy and weakness, which led to a fall and T10–T12 vertebral fractures. After, she was transferred to an inpatient rehab facility. Her ketoconazole dosage was uptitrated to 400 mg twice daily; however, the facility was unable to complete repeat cortisol lab testing, so a response to therapy was not available. The patient then developed septic shock secondary to a perforated colon and required emergent exploratory laparotomy with partial colon resection. Her hospitalization was complicated by wound dehiscence at her surgical sites (Fig. 3) and acute respiratory distress syndrome requiring intubation. Given her critical illness and continued hypercortisolemia, she underwent CT-guided cryoablation of the carcinoid tumor with subsequent morning cortisol of 25.6 ug/dL (Table). Regrettably, the patient had declining respiratory status, and her family decided to withdraw care. She passed away less than 4 months after her initial hospitalization at our institution.

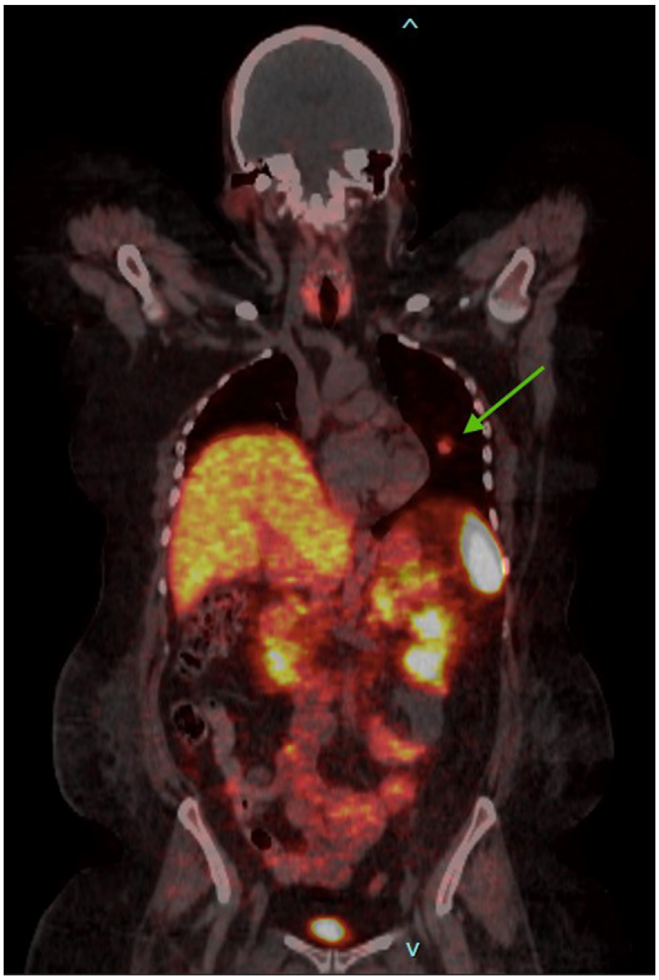

Fig. 2. Dotatate scan showing a 1.6 × 1.4 cm avid *left* pulmonary nodule (green arrow); no noted avidity in axillary, mediastinal, or hilar lymph nodes.

Discussion

Our patient developed rapid onset and severe symptoms of hypercortisolemia over a 3-month period in the setting of a biopsy-proven typical pulmonary carcinoid tumor. The clinical manifestation of severe and rapid EAS is unusual with a diagnosis of typical pulmonary carcinoid and is usually seen in higher-grade NETs or metastatic disease.[1] This led to the decision to evaluate for metastases prior to surgical resection. Unfortunately, the patient suffered from complications related to hypercortisolemia despite medical therapy and eventually passed.

Pulmonary carcinoid tumors are rare, with an age-adjusted incidence rate of 0.5 to 0.7/100,000 population/year.[6,7] Rates of pulmonary carcinoid are higher in Caucasians, and women are

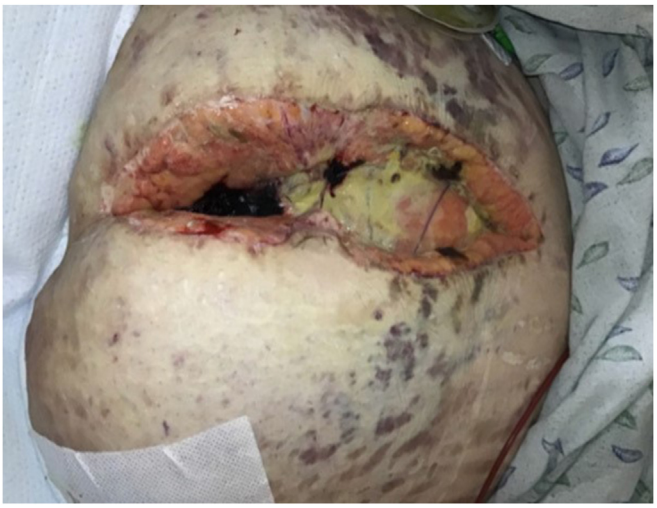

Fig. 3. Photograph of the patient showing dehiscence of her midline abdominal incision after exploratory laparotomy.

slightly more affected.[6,7] Pulmonary carcinoid typically occurs in the fourth to sixth decades of life, younger than in higher grade NETs.[6,7] EAS occurs in 6% of patients with pulmonary carcinoid, which is the most common type of ACTH-secreting tumor (>25%), followed by SCLC (20%).[3,8]

Lung NETs are classified by pathologic severity from well-differentiated (low-grade typical pulmonary carcinoids and intermediate-grade atypical carcinoids) to poorly differentiated (high-grade large cell neuroendocrine carcinoma and SCLC).[9] High-grade NETs are shown to present with higher levels of cortisol than low-grade NETs (2400 nmol/L vs 1100 nmol/L) and require admission sooner from the time of symptom onset (3 months vs 12 months).[1]

The classic symptoms of Cushing's syndrome include muscle weakness (79%), hypokalemia (72%), body weight changes (69%), truncal obesity (66%), full moon face (66%), hypertension (59%), and diabetes (59%).[8] These typical features are more frequent in well-differentiated tumors, whereas more aggressive histologic types present more commonly with hyperpigmentation, weight loss, and mineralocorticoid effects.[3,5]

Tumor resection is the mainstay of therapy in patients with EAS who have an identifiable tumor source as it can achieve rapid eucortisolemia and lead to cure in >80% of cases.[1-5,10] The 5-year survival after resection is up to 90% in patients with localized typical pulmonary carcinoid tumors.[11] Typical pulmonary carcinoid tumors are usually indolent with a low rate of metastases, reported in <15% of cases.[3,10,12,13] However, when pulmonary carcinoids produce ACTH, they have been shown to have a higher rate of nodal metastases and may require further evaluation prior to surgery or more extensive exploratory surgery.[14]

For patients who are unable to undergo surgery due to tumor location or medical comorbidities, tumors may be amenable to image-guided percutaneous ablation. Radiofrequency ablation (RFA), microwave ablation, and cryoablation are being more widely used in clinical practice. Cryoablation has been shown to have complete tumor removal in nearly 30% of patients in one retrospective study.[15] RFA for EAS due to pulmonary carcinoid has also been reported in the literature with achievement of eucortisolemia[16]; however, no large studies of outcomes have been completed at the time of this literature review.

In our case, surgery was not an option due to our patient's rapid decline; thus, cryoablation was pursued. Following the ablation, her morning serum cortisol level was 25.6 ug/dL; unfortunately, a preoperative level was not measured. This repeat cortisol level was below her initial baseline value and lower than both the low and high dose DST levels. This may be an indication she had some improvement in her hypercortisolemia after cryoablation therapy.

Our case highlights the wide range of severity that can be present in EAS due to typical pulmonary carcinoid. Key findings in our case are the significantly elevated cortisol at presentation, the rapid onset of Cushing's syndrome over a 3-month period, and the severity of symptoms, which led to significant morbidity and mortality. This presentation was more typical of an aggressive, poorly differentiated NET versus a well-differentiated pulmonary carcinoid.

Conclusion

This case demonstrates that typical pulmonary carcinoid tumors can present with rapid and severe onset hypercortisolemia. While metastatic disease is rare, it is found in up to 15% of cases. The decision to obtain further imaging to evaluate for metastatic disease should be considered. However, patients with severe hypercortisolemia may benefit from immediate resection to achieve eucortisolemia.

Disclosure

The authors have no conflicts of interest to disclose.

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