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Case Report

Finding the Culprit: Cushing Syndrome Secondary to Lung Carcinoid Tumor

Richard Vaca, MD [1], Nirali A. Shah, MD [2,*]

[1] Division of Internal Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, New York
[2] Division of Endocrinology, Diabetes and Bone Disease, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

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ABSTRACT

Background/Objective: Cushing syndrome resulting from ectopic adrenocorticotropic hormone (ACTH) secretion (EAS) is a rare condition, and its occurrence in adolescents is even more uncommon, representing <1% of cases. We describe a case of EAS from a lung carcinoid tumor leading to Cushing syndrome in a young woman, which was successfully treated with excision of the tumor.
Case Report: An 18-year-old woman presented with mood disturbances, weight gain, and fatigue for 6 months. Workup revealed high levels of urinary free cortisol (>900 μg/dL; normal range, <45 μg/dL) and midnight salivary cortisol (0.755 μg/dL; normal range, <0.09 μg/dL). The ACTH and cortisol levels remained elevated after a low-dose dexamethasone suppression test. Magnetic resonance imaging of the pituitary gland did not reveal any adenoma and inferior petrosal sinus sampling showed no central-to-peripheral gradient. A diagnosis of EAS was made. Subsequent body imaging noted a 1-cm lung nodule. Due to symptoms of severe hypercortisolism including hypokalemia and worsening mood changes, the patient was started on metyrapone as a bridge to surgery. A few weeks later, the patient underwent successful surgical resection, after which symptoms promptly resolved. Pathology report later confirmed an atypical lung carcinoid tumor. The patient remained in remission at 1-year follow-up.
Discussion: Medical therapy aids in managing severe hypercortisolism in ACTH-secreting tumors until definitive surgical treatment can be undertaken.
Conclusion: This case underscores the critical importance of promptly recognizing EAS and the resulting severe hypercortisolism symptoms because early surgical intervention can lead to a cure.
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Introduction

Cushing syndrome (CS) from ectopic adrenocorticotropic hormone (ACTH) secretion (EAS) is a rare condition and is even rarer in adolescents, representing <1% of CS cases.[1] EAS is associated with a wide range of complications. The clinical manifestations can vary depending on factors such as age, tumor characteristics, and the intensity and duration of hypercortisolism.

Case Report

An 18-year-old woman presented with weight gain, anxiety, heat intolerance, and fatigue. Her father had noticed facial bloating for the past 6 months. She denied any skin changes, acne, or hirsutism. She had no medical history and was previously on oral contraceptive pills but had stopped 1 month before initial presentation. She denied use of any other medication. Physical examination was notable for purple striae, facial plethora, and buffalo hump on the neck. Vital signs including blood pressure were normal. Initial workup showed an increased urinary free cortisol (UFC) level (>900 μg/dL [normal range {nr}, <45 μg/dL]), and the levels of midnight salivary cortisol in 2 samples increased (0.476 and 0.755 μg/dL [nr, <0.09 μg/dL]). Her early morning cortisol level was 27.5 μg/dL (nr, 6.2-19.4 μg/dL) with an ACTH level of 29.5 pg/mL (nr, 7.2-63.3 pg/mL). An overnight 1-mg dexamethasone suppression test revealed a persistently increased cortisol level of 24.8 μg/dL which led to a diagnosis of ACTH-dependent CS. The results of the rest of

Abbreviations: ACTH, adrenocorticotropic hormone; CS, Cushing syndrome; CT, computed tomography; EAS, ectopic adrenocorticotropic hormone secretion; IPSS, inferior petrosal sinus sampling; nr, normal range; PET, positron emission tomography; TTF-1, thyroid transcription factor 1; UFC, urinary free cortisol.

* Address correspondence to Dr Nirali A. Shah, Division of Endocrinology, Diabetes and Bone Disease, Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1055, New York, NY 10029.
E-mail address: nirali.shah@mssm.edu (N.A. Shah).

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the hormonal panel were as follows: (1) prolactin level, 16.4 ng/mL (nr, 4.8-23.3 ng/mL); (2) follicle-stimulating hormone level, 3.1 mIU/mL; (3) luteinizing hormone level, 2.3 mIU/mL; (4) thyroid-stimulating hormone level, 1.150 μIU/mL (nr, 0.450-4.500 μIU/mL); (5) free thyroxine level, 1.20 ng/dL (nr, 0.93-1.60 ng/dL); and (6) hemoglobin A1c level, 5.6% (38 mmol/mol).

Pituitary magnetic resonance imaging revealed a heterogeneous pituitary but no definitive adenoma (Fig. 1). Later, she underwent inferior petrosal sinus sampling (IPSS). The values obtained for the patient showed a central-to-peripheral gradient of 1.76, with no significant change after desmopressin stimulation. A 24-hour UFC sample collected on the same day of the procedure confirmed active excess cortisol secretion (>900 μg/dL [nr, <45 μg/dL]). An IPSS central-to-peripheral ACTH gradient of <2 before or <3 after stimulation suggests EAS.[2,3] Based on our patient's IPSS gradient, a diagnosis of EAS was made, and additional imaging was performed.

Chest computed tomography (CT) with contrast revealed a 1-cm enhancing nodule at the right upper lung. Subsequent positron emission tomography (PET)/CT did not show any additional areas of increased radiotracer activity other than the lung nodule (Fig. 2).

The patient developed hypokalemia (potassium level, 2.5 mEq/L), 3.6-kg weight gain, and symptoms of insomnia and depression concerning for severe hypercortisolism within 4 weeks of presentation. She was started on medical therapy as a bridge to surgery with ketoconazole, spironolactone for hypokalemia, atovaquone for *Pneumocystis jirovecii* prophylaxis, and apixaban for deep vein thrombosis prevention. The patient subsequently developed hepatotoxicity with increased levels of alanine aminotransferase of 114 IU/L and aspartate aminotransferase of 49 IU/L; therefore, ketoconazole was replaced by metyrapone, after which the results of the liver function tests normalized.

She underwent wedge resection of the tumor, and pathology showed a 1-cm × 0.7-cm × 0.6-cm tumor with no lymphovascular or visceral pleural invasion. Immunostaining showed tumor cells to be positive for CAM5.2 and synaptophysin, with a proliferative index of <2% by Ki-67. Immunostaining for S-100 outlined periphery of tumor nests, whereas immunostaining for thyroid transcription factor 1 (TTF-1) was negative. The mitotic rate was low with <1 mitosis/mm^2; however, presence of focal punctate necrosis was consistent with diagnosis of atypical carcinoid tumor (Fig. 3).

Following nodule resection, electrolyte disturbances resolved, and spironolactone was stopped within 1 week of surgery. Her anxious mood, depression, and inability to concentrate improved over the next few weeks. She was started on hydrocortisone 20 mg in the morning and 10 mg in the afternoon, which was tapered down after 2 months. She was maintained on apixaban for 4 weeks. At the 2-month follow-up, the morning cortisol and ACTH levels were within normal limits, and glucocorticoids were discontinued.

Highlights

- ACTH secretion is suspected after IPSS excluded a central source
- CT scan of the lungs, neck, and mediastinum can identify most ACTH-secreting tumors
- Ketoconazole and metyrapone can help suppress hypercortisolism in ectopic Cushing

Clinical Relevance

We also emphasize the need for a comprehensive diagnostic approach in ectopic Cushing syndrome and the need for prompt diagnosis and intervention, including considering medical therapy until definitive surgical treatment.

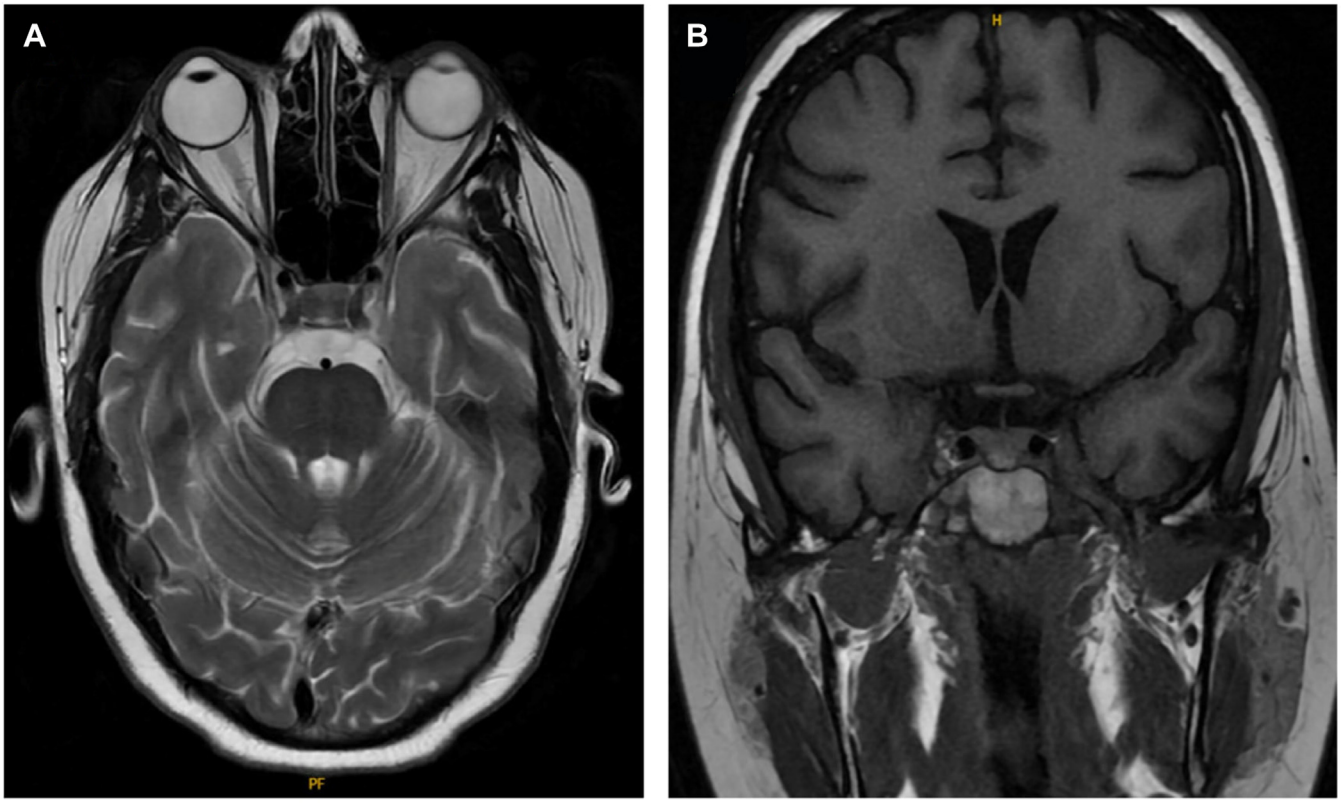

Fig. 1. Pituitary magnetic resonance imaging showing pituitary heterogeneous hypoenhancement but no mass in axial view (*A*) and no suprasellar mass in coronal view (*B*).

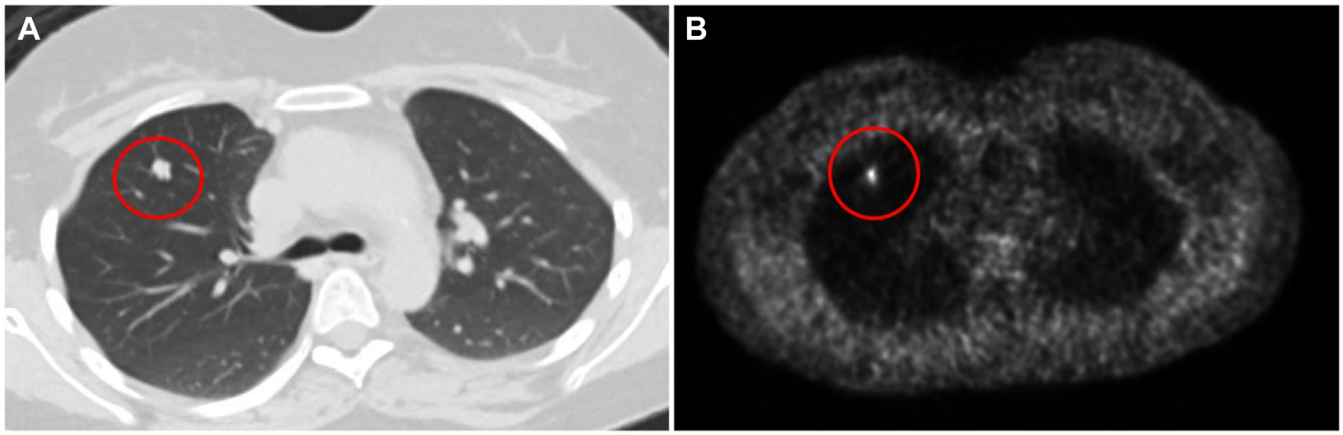

Fig. 2. Chest computed tomography scan notable for a 1-cm right upper lobe nodule (*A*) subsequently analyzed by gallium-68 DOTATATE positron emission tomography computed tomography (*B*) identifying it as a mildly radiotracer-avid lung nodule.

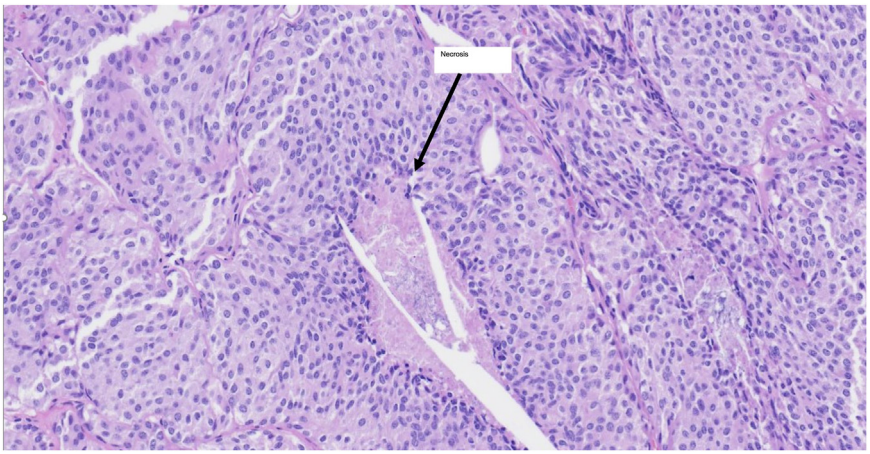

Fig. 3. The mitotic rate was low with <1 mitosis/mm^2; however, the presence of focal punctate necrosis was consistent with diagnosis of atypical carcinoid tumor.

At the 12-month follow-up, patient demonstrated remarkable mood improvement along with a 20-kg weight loss, improvement in features, and muscle strength. Blood pressure remained at normal levels. The cortisol, ACTH, glucose, and electrolytes levels remained normal, and chest CT did not reveal any recurrence of the tumor.

Discussion

We present a rare case of EAS from a lung carcinoid tumor leading to CS in a young woman. This case underscores the importance of recognizing this condition because early intervention can lead to complete remission as demonstrated in our case. Occasionally, medical management may be necessary as a bridge to surgical treatment when patients present with severe Cushing symptoms.

Some CS cases have a rapid CS progression and may present with severe symptoms including muscle weakness, hypokalemia, venous thromboembolism, psychiatric disturbances (eg, anxious mood, depression, and psychosis), opportunistic infections, hypertension, and hyperglycemia.[4-6] Laboratory findings can also suggest severe hypercortisolism especially a UFC level fourfold or fivefold above the upper limit of normal, a morning cortisol level of >40 μg/dL (1100 nmol/L), and/or severe hypokalemia, which is the hallmark of severe CS because hypercortisolism causes a spillover effect on the mineralocorticoid receptor activating it, resulting in a pseudohyperaldosteronism state. This effect is mediated by an oversaturation of the 11-beta hydroxysteroid dehydrogenase type 2 enzyme, which normally removes a hydroxyl group from cortisol, therefore inactivating it to cortisone, which is not a ligand to the mineralocorticoid receptor at the renal collecting ducts.[7,8] In severe hypercortisolism, this enzyme becomes saturated by increased cortisol plasma levels,[9] and other authors have also proposed a direct effect of ACTH or other adrenal steroids on the decreased enzyme activity.[10] Our patient presented with an increased UFC level, hypokalemia, and mood disorder suggesting severe disease.

Early initiation of treatment for CS is likely to yield better outcomes. However, historically, the prognosis of EAS has been reported as poor, particularly in cases where malignant features are observed in pathology samples. More recently, increased mortality has been associated with multiple hormone secretion, a Ki-67 index >20%, TTF-1−negative tumors, and diabetes.[11] TTF-1, heavily expressed in type 2 alveolar cells, in some studies has shown to have a favorable prognostic value in certain lung adenocarcinomas.[12] Other studies have shown TTF-1 expression to be highly specific but not sensitive for pulmonary neuroendocrine tumors.[13,14] Prophylaxis against Pneumocystis needs to be considered if the UFC level significantly increases (ie, >5 to 10 times the upper limit of normal).[14] Venous thromboembolism prophylaxis also needs individualized risk assessment and should be considered if there are concomitant risk factors.[2]

Localizing the tumor in EAS is challenging. Because these cases typically manifest with severe hypercortisolism, diagnostic strategies are expedited. After diagnosing ACTH-dependent hypercortisolism, IPSS is recommended to distinguish between central

secretion and ectopic secretion; although this test has high diagnostic accuracy for localization to the pituitary gland, it is not sufficiently reliable for tumor lateralization to the right or left side of the gland.[2,3] However, this test is not readily accessible due to its invasive nature, need for an experienced interventional radiologist, and its associated procedural complexities.[15] Other modalities in diagnosis include high-dose dexamethasone suppression test and/or stimulation test with corticotropin-releasing hormone or desmopressin. The utility of these tests relies on the presence of overexpressed corticotropin-releasing hormone and desmopressin receptors in patients with CS but not in those with EAS.[2] It has been shown that a combination of tests has better yield than a single diagnostic test.[16]

There is no clear consensus on whether whole-body imaging should precede IPSS. However, in instances where IPSS is not readily available, whole-body imaging should be considered as the initial step because of its noninvasive nature. Two primary modalities for imaging are available: (1) functional imaging techniques such as Octreoscan, gallium-68–labeled somatostatin analog PET/CT, or fluorine-18 fludeoxyglucose PET/CT and (2) whole-body CT, with particular focus on the neck, lungs, and mediastinum because of its high sensitivity in identifying tumors.

The choice of imaging modality is unclear, with most opting for whole-body CT followed by functional studies. Nuclear imaging tests are preferred in cases where CT fails to detect a tumor because they offer 100% sensitivity in such instances.[17] Imaging not only aids in confirming the diagnosis but also provides a roadmap for surgical excision, which is particularly valuable given the urgency to remove the tumor.

Surgery is the cornerstone of CS treatment because it can lead to rapid resolution of symptoms. However, surgery may need to be delayed in cases of severe electrolyte disturbances, refractory hypertension, hyperglycemia, altered mental status, or sepsis. Medical treatment should not be delayed in such cases or when there is severe hypercortisolism syndrome.

Medical treatment in severe hypercortisolism includes adrenal steroidogenesis inhibitors as first line.[5] Current guidelines and expert consensus recommend metyrapone and ketoconazole as first line agents based on effectiveness and rapidity of action.[4,18] However, metyrapone is generally used off-label because it is not currently approved by the U.S. Food and Drug Administration. Metyrapone is preferred due to rapid onset of action because the effect can be seen within 24 hours; however, hypokalemia may occur due to accumulation of 11-deoxycortisol. Ketoconazole takes longer to act, with effects observed within 1 week of therapy, with transaminitis as a possible side effect.[19] Etomidate can have a special role in critically ill patients who are not stable for surgery in the short term, where its intravenous administration can be crucially beneficial.[4] Patients with severe hypercortisolism should also receive prophylaxis against opportunistic infection such as that caused by Pneumocystis because cortisol can affect both the innate and adaptive immune systems. Unprovoked venous thromboembolism can occur in up to 2.5% of CS due to activation of the coagulation cascade by cortisol persisting up to 4 weeks postoperatively; therefore, guidelines recommend perioperative thromboprophylaxis.[4,20]

The patient's remarkable clinical improvement, including weight loss and mood enhancement, underscores the importance of prompt diagnosis and treatment of ectopic ACTH-secreting tumors given the likelihood of complete resolution of symptoms.

Conclusion

In conclusion, this case emphasizes the need for a comprehensive diagnostic approach in patients presenting with ectopic CS and the need for prompt diagnosis and intervention.

Statement of Patient Consent

The authors obtained an informed consent from the patient.

Disclosure

The authors have no conflicts of interest to disclose.

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