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Case Report

Cushing Syndrome Due to a Corticotropin-Releasing Hormone– and Adrenocorticotropic Hormone–Secreting Silent Pheochromocytoma

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ABSTRACT

Background/Objective: Ectopic cosecretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) in silent (ie, non–catecholamine-secreting) pheochromocytoma is a rare cause of Cushing syndrome.
Case Report: A 57-year-old woman rapidly developed hypercortisolism, clinically manifesting as fatigue, muscle weakness, weight gain, and worsening hypertension and biochemically characterized by hypokalemia and marked increases in the serum cortisol and plasma ACTH levels. This acute presentation suggested a diagnosis of ectopic ACTH syndrome (EAS). Imaging studies revealed a right adrenal mass that enhanced after administration of the radioisotope gallium-68-DOTATATE. Plasma metanephrines were normal in 2 separate measurements. The possibility of a silent pheochromocytoma was considered. After controlling her hypercortisolism with metyrapone and surgical preparation with alpha blockade, the patient underwent elective right adrenalectomy. Pathology revealed a pheochromocytoma that stained focally for ACTH and CRH. Postoperatively, the cortisol levels normalized, the hypothalamic-pituitary-adrenal axis was not suppressed, and clinical symptoms from hypercortisolism abated.
Discussion: Patients who exhibit a rapid progression of ACTH-dependent hypercortisolism should be screened for EAS. The use of functional imaging radioisotopes (eg, gallium DOTA-peptides) improves the detection of ACTH-secreting tumors. Preoperative treatment with steroidogenesis inhibitors helps control clinical and metabolic derangements associated with severe hypercortisolemia, whereas alpha blockade prevents the onset of an adrenergic crisis.
Conclusion: We present a rare case of EAS due to a silent pheochromocytoma that cosecreted ACTH and CRH. Pheochromocytoma should be considered in patients with EAS who have an adrenal mass even in the absence of excessive catecholamine secretion.

Introduction

Cushing syndrome (CS) is rare, with an estimated incidence of 0.2 to 5.0 per million people per year and prevalence of 39 to 79 per million.[1] Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS), a type of CS originating from extrapituitary ACTH-secreting tumors, is uncommon. The prevalence of CS due to ACTH-secreting adrenal medullary lesions is not well established. However, EAS is observed in approximately 1.3% of all identified cases of pheochromocytoma.[2] Recognizing EAS can be challenging because of its rarity, leading to delayed diagnosis.

Neuroendocrine neoplasms can produce corticotropin-releasing hormone (CRH), which can lead to the secretion of ACTH by the pituitary. In certain cases, cosecretion of ACTH and CRH by an adrenal neoplasm has been observed. Only 2 published cases have provided definitive biochemical and immunohistochemical evidence of exclusive CRH secretion.[3]

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CS, Cushing syndrome; CT, computed tomography; EAS, ectopic adrenocorticotropic hormone syndrome; HPA, hypothalamic-pituitary-adrenal; PET, positron emission tomography; ^{68}Ga, gallium-68.

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Case Report

A 57-year-old woman with a history of well-controlled hypertension sought care because of a 2-month history of a 60-lb weight gain, facial rounding, easy bruising, muscle weakness, lower extremity edema, and acne. Her blood pressure control had worsened, and the laboratory tests showed a markedly low serum potassium level of 1.8 mmol/L while taking hydrochlorothiazide. To manage her blood pressure, she was prescribed a calcium channel blocker, an angiotensin receptor blocker, and potassium supplements. However, her symptoms worsened, and she was referred to our emergency department. Her blood pressure at presentation to our hospital was 176/86 mm Hg. She had characteristic features of CS, including face rounding, supraclavicular fullness, dorsocervical fat accumulation, pedal edema, oral candidiasis, multiple forearm ecchymoses, and acneiform skin eruptions. No visible abdominal striae were present. She had no family history of pheochromocytoma or multiple endocrine neoplasia type 2.

The serum cortisol level was 128 mcg/dL (normal range, 4.6-23.4 mcg/dL) at 5 PM, with an ACTH level of 1055 pg/mL (normal range, 6-50 pg/mL); the serum dehydroepiandrosterone sulfate level increased at 445 mcg/dL (normal range, 8-188 mcg/dL). Her 24-hour urine cortisol level was 12 566 mcg (normal range, 4.0-50.0 mcg). The plasma metanephrine level was normal at <25 pg/mL (normal range, <57 pg/mL), and the plasma normetanephrine level was 44 pg/mL (normal range, <148 pg/mL). A second plasma metanephrine measurement showed similar results. The serum aldosterone level and plasma renin activity were low at 2 ng/dL (normal range, 3-16 ng/dL) and 0.11 ng/mL/hour (normal range, 0.25-5.82 ng/mL/hour), respectively. The dopamine and methoxytyramine levels were not measured. Abdominal computed tomography (CT) revealed a 4.8 × 4.5 × 5–cm right heterogeneously enhancing adrenal mass with a mean Hounsfield unit of 68 in the noncontrast phase and an absolute percentage washout of 30% (Fig. 1 *A*). The left adrenal gland appeared hyperplastic (Fig. 1 *B*). An Octreoscan, which was the in-hospital available nuclear medicine imaging modality, confirmed a 5.1-cm adrenal mass that was mildly to moderately avid, with diffuse bilateral thickening of the adrenal glands and no other focal radiotracer avidity. Pituitary magnetic resonance imaging did not show an adenoma, and EAS was suspected. Further evaluation with gallium-68 (^{68}Ga)-DOTATATE positron emission tomography (PET)/CT (Fig. 2) was performed after her admission demonstrated an avid right adrenal mass consistent with a somatostatin receptor–positive lesion. No other suspicious tracer uptake was detected. These findings were consistent with a neuroendocrine tumor, such as pheochromocytoma.

To control her symptoms while undergoing workup, the patient received oral metyrapone 500 mg thrice daily and oral ketoconazole 200 mg twice daily. Ketoconazole was stopped because of an increase in the transaminase levels. The dosage of metyrapone was increased to 500 mg 4 times daily and later decreased to alternating doses of 250 and 500 mg 4 times daily. Within 3 weeks of starting medical therapy, the serum cortisol level normalized at 20 mcg/dL. The 24-hour urinary free cortisol improved to 246.3 mcg/24 hours. She experienced gradual improvement in facial fullness, acne, and blood pressure control.

The possibility of a silent pheochromocytoma was considered, and α-adrenergic blockade with doxazosin 1 mg daily was started 1 month before surgery. She underwent surgery after 2 months of metyrapone therapy. With an unclear diagnosis and a large, heterogeneous adrenal mass, the surgical team elected to perform open adrenalectomy for en bloc resection because of concerns for an adrenal malignancy. The tumor was well demarcated and did not invade the surrounding structures (Fig. 3 *A*). Hematoxylin and eosin–stained sections showed classic morphologic features of a pheochromocytoma (Fig. 3 *B*), with immunohistochemistry demonstrating strong immunoreactivity for synaptophysin and chromogranin and negative steroidogenic factor 1 and inhibin stains excluding an adrenal cortical lesion. The sections analyzed by QuPath[4] revealed that approximately 4% of cells were ACTH cells, often found in isolation, and had a clear, high signal-to-noise staining (Fig. 3 *C*).

CRH cells were less prevalent, comprising approximately 2.4% of the total analyzed cells, and tended to cluster together (Fig. 3 *D*). These cells had more background staining, resulting in a lower signal-to-noise ratio.

The patient's postoperative recovery was uneventful, with a short course of hydrocortisone that was stopped 1 week after surgery after the hypothalamic-pituitary-adrenal (HPA) axis evaluation showed normal results. After 1 month, hypercortisolism had resolved, as shown by a normal 24-hour urinary free cortisol at 28 mcg.

Administration of dexamethasone at 11 PM resulted in suppression of morning cortisol to 0.8 and 0.6 mcg/dL 1 and 7 months after surgery, respectively. Her liver function test results normalized, and her blood pressure was well controlled with amlodipine 10 mg daily and losartan 100 mg daily. Genetic testing for pheochromocytoma predisposition syndromes is currently planned.

Highlights

- Ectopic ACTH secretion should be considered in severe ACTH-dependent Cushing
- ACTH secretion by a pheochromocytoma should be suspected with an adrenal mass
- Medical management can be initiated when severe hypercortisolemia is present
- Prolonged medical therapy for cases where the ACTH source cannot be identified
- Adrenalectomy is indicated for ACTH-/CRH-secreting pheochromocytomas

Clinical Relevance

This case highlights the importance of considering ectopic adrenocorticotropic hormone (ACTH) secretion by a pheochromocytoma in patients presenting with rapid progression and considerable clinical hypercortisolism concomitant with an adrenal mass and increased plasma ACTH level. This represents an unusual manifestation of a specific subtype of an ACTH-/corticotropin-releasing hormone–secreting pheochromocytoma that did not exhibit catecholamine secretion.

Discussion

EAS accounts for 10% to 20% of cases of ACTH-dependent CS.[5] This condition can be caused by several neuroendocrine neoplasms that produce bioactive ACTH.[6] In the literature, we have found 99 documented cases of EAS caused by a pheochromocytoma. Of these, 93% showed ACTH expression. Only 2 cases have been reported with dual staining of ACTH and CRH.[7]

Exclusive CRH production has only been reported in 2 cases.[8,9] However, the true prevalence of CRH-producing pheochromocytomas may be underestimated because in most cases, testing for CRH expression was not performed.

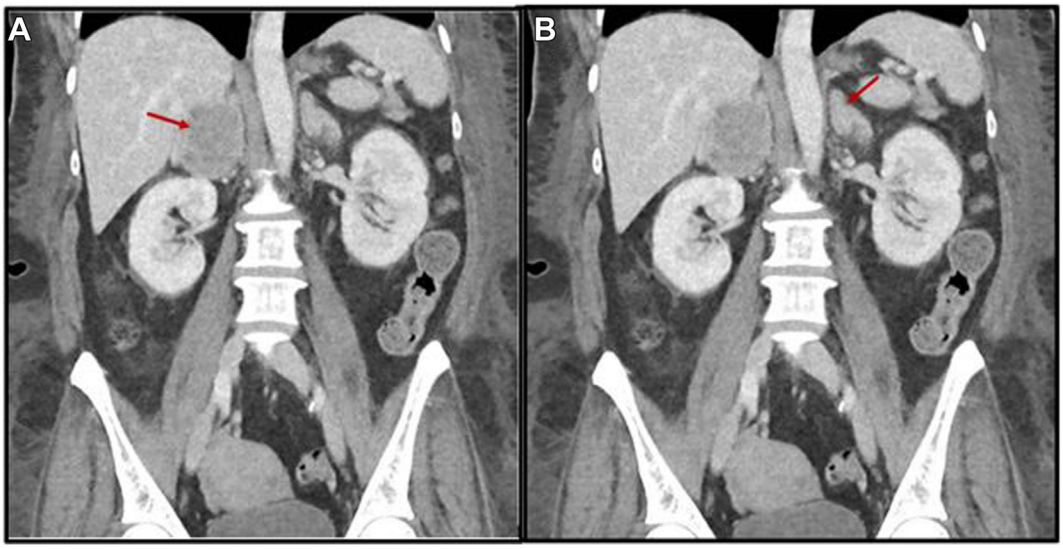

Fig. 1. Preoperative abdominal computed tomography scan showing a 4.8 × 4.5 × 5–cm right heterogeneously enhancing adrenal mass with irregular borders (*A*) and a hyperplastic left adrenal gland (*B*).

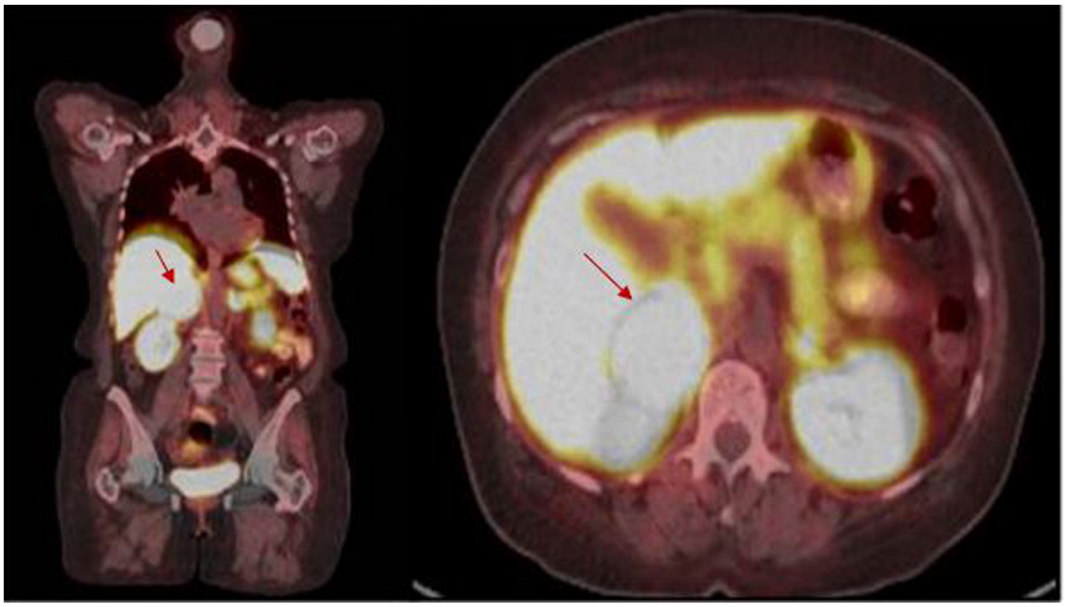

Fig. 2. Gallium-68-DOTATATE positron emission tomography/computed tomography showing an avid right adrenal mass.

Although the clinical presentation of EAS may be highly variable, there is often a rapid onset of hypercortisolism accompanied by severe catabolic symptoms. The diagnostic process should focus on identifying the location of a potential neuroendocrine neoplasm responsible for the ACTH secretion. Sometimes, the peripheral origin of ACTH should be confirmed by inferior petrosal sinus sampling. In this case, given the clinical presentation consistent with EAS, negative pituitary magnetic resonance imaging result, and presence of an adrenal mass that needed to be removed independently, inferior petrosal sinus sampling was not performed.

Neuroendocrine neoplasms express somatostatin receptors on their surface, which allow functional imaging using indium-111-pentetreotide (Octreoscan). However, Octreoscan has a low sensitivity in detecting occult EAS. In cases where the tumor is in the abdomen and pelvis, Octreoscan has limited utility in locating the source of ACTH.[10] This increased risk of false negatives is caused by physiological tracer uptake by the liver, spleen, urinary tract, bowel, and gallbladder. The use of ^{68}Ga-labeled somatostatin receptor ligands (PET/CT ^{68}Ga-DOTATATE) is more effective in detecting somatostatin receptors (SSTR2) than indium-111-pentetreotide because of its higher spatial resolution and affinity.[11] This test was performed after discharge from the hospital to rule out the presence of a second smaller neuroendocrine tumor that the Octreoscan may have missed. A new molecular imaging technique targeting CRH receptors (^{68}Ga CRH PET/CT) has shown potential in identifying tumors expressing CRH; however, its availability remains limited.[12] In our patient's case, both the Octreoscan and ^{68}Ga-DOTATATE successfully identified the adrenal tumor as a potential ACTH/CRH secretion source.

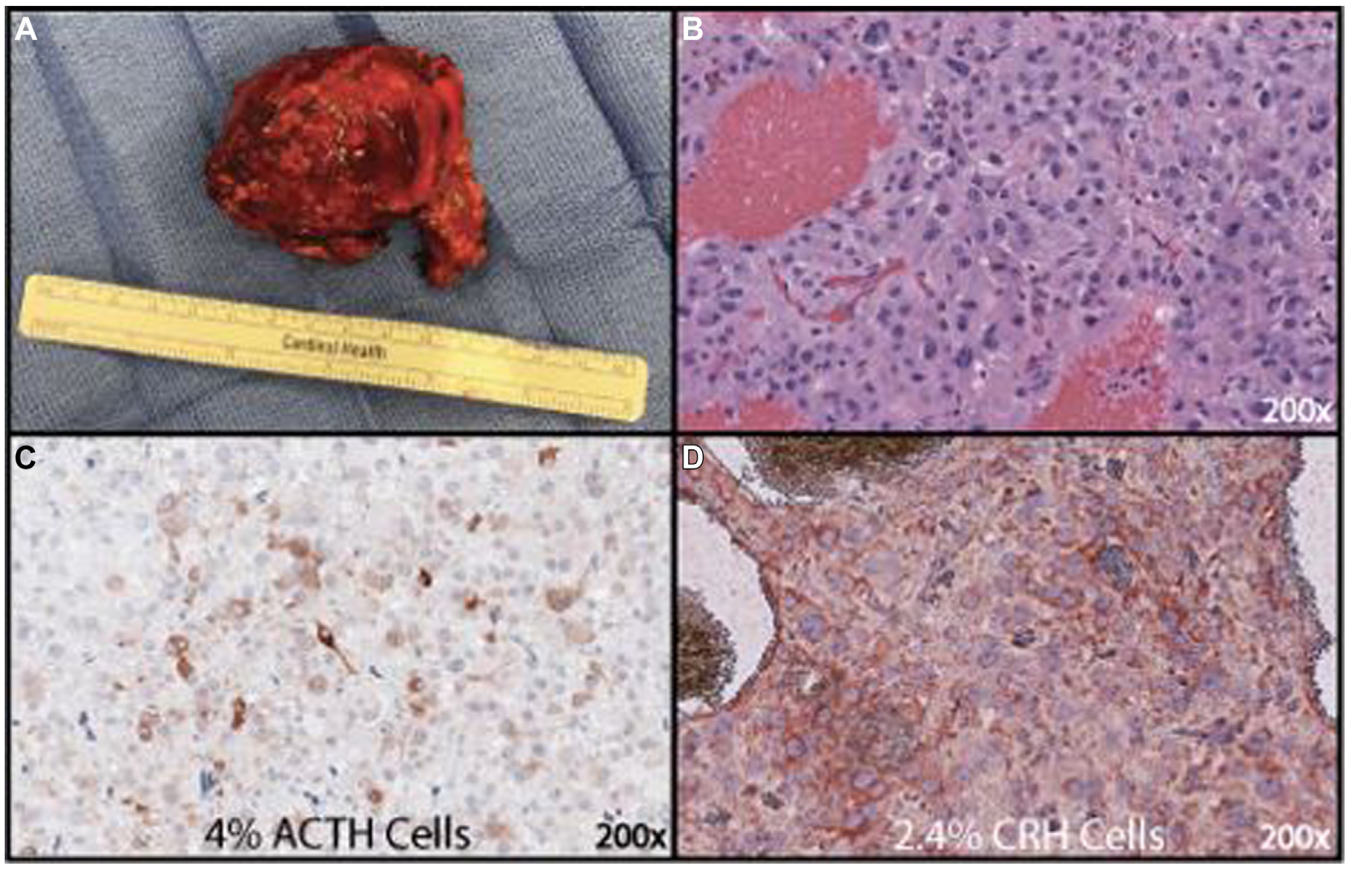

Fig. 3. Gross and histopathologic analysis of the patient's pheochromocytoma. *A*, Image of the gross excised specimen. *B*, Hematoxylin and eosin staining (final magnification, ×200) demonstrated prominent vascularity and cells with finely granular, eosinophilic cytoplasm and salt-and-pepper chromatin. *C*, Adrenocorticotropic hormone staining (final magnification, ×200) showed clear and isolated positive cells, representing approximately 4.0% of the section analyzed by QuPath. *D*, Corticotropin-releasing hormone staining (final magnification, ×200) revealed tight clusters of positive cells, accounting for 2.4% of the total cells. Positive (human placenta and hypothalamus) and negative (thyroid gland) control tissues performed as expected (data not shown).

According to relevant guidelines, presurgical adrenergic blockade is recommended for patients with biochemical evidence of catecholamine excess.[13,14] Conversely, silent pheochromocytomas can generally be operated without alpha blockade.[15] Despite this, we opted to administer preoperative alpha blockade as a precautionary measure for this patient.

Pathology examination confirmed the diagnosis of pheochromocytoma. ACTH and CRH staining demonstrated that clear and significant populations of 2 separate ACTH- and CRH-positive cells were present in the excised pheochromocytoma. ACTH/CRH cells were dispersed throughout various regions of the pheochromocytoma rather than being well-defined, separate histologic entities. As a result, there is no indication that this resulted from collision tumors but rather random mutation and expansion of tumor cells into ACTH- or CRH-secreting cells. These results have limitations, including variation in ACTH- and CRH-expressing regions because of tumor heterogeneity, nonspecific binding of polyclonal antibodies, and normal low-rate false-negative/false-positive detection using QuPath.

The postsurgical normal HPA activity was likely due to the desuppression of the HPA axis by medical therapy; however, it may also be explained by chronic stimulation of corticotroph cells induced by ectopic CRH secretion.

The standard approach to managing EAS involves surgical intervention. However, surgery may not be a viable option in cases where the source of ACTH production is unknown. Medical therapy to reduce or block excess cortisol can be used in such circumstances.

Conclusions

In conclusion, a pheochromocytoma causing EAS should be considered even in the absence of increased plasma metanephrine levels. These tumors may simultaneously express ACTH and CRH.

Disclosure

The authors have no conflicts of interest to disclose.

Author Contributions

S.M. and J.L.P. contributed equally.

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