Cushing's Syndrome Due to Ectopic Adrenocorticotrophic Hormone Production Secondary to Hepatic Carcinoid: Diagnosis, Treatment, and Improved Quality of Life

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INTRODUCTION: We describe a previously healthy 40-year-old woman with Cushing's syndrome caused by adrenocorticotrophic hormone (ACTH) secretion from metastatic carcinoid.

CASE REPORT: Over a 2-year period, the patient had multiple hospitalizations for uncontrolled hypertension, hyperglycemia, and hypokalemia. She had transient flushing, rashes, and a rapid weight gain. In addition, she developed anasarca and had a nontraumatic hip fracture 1 month before presentation. Subsequently, a hypertensive crisis resulted in admission to the intensive care unit and fine-needle aspiration of a liver lesion.

DISCUSSION: A diagnosis of metastatic carcinoid was established. She was transferred to our hospital for further evaluation and management. On arrival, she had the signs of Cushing's syndrome. Despite extensive evaluation, her primary carcinoid tumor was not localized. She was treated successfully with bilateral adrenalectomy and octreotide.

CONCLUSION: This case illustrates how early recognition of the signs and symptoms of excess ACTH is important for prompt and appropriate treatment.

KEY WORDS: carcinoid; corticotropin; Cushing's disease; Cushing's syndrome; ectopic adrenocorticotrophic hormone; neuroendocrine tumor.

Abbreviations

ACTH	adrenocorticotrophic hormone
CRH	corticotropin-releasing hormone

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INTRODUCTION

Cushing's syndrome secondary to ectopic adrenocorticotrophic hormone (ACTH or corticotropin) production has been well-described in the literature. We present a patient with Cushing's syndrome caused by ACTH from a carcinoid metastatic to the liver, a rare cause of Cushing's syndrome.

REPORT OF A CASE

A 40-year-old female was transferred to our hospital for management of a newly diagnosed carcinoid. She had been relatively healthy until 2 years earlier when she began to develop progressively difficult to control hypertension, hyperglycemia, and hypokalemia. Over the course of 2 years, she had been hospitalized multiple times at an outside facility. During one of her hospitalizations, an abdominal ultrasound was obtained that showed 3 liver lesions; however, their clinical importance was unknown at the time, therefore, no further workup was done. A hypertensive crisis prompted her most recent admission to an intensive care unit. Fine-needle aspiration of one of her liver lesions revealed carcinoid and she was transferred to Mayo Clinic Jacksonville for further management.

Upon questioning, the patient described transient episodes of flushing, rashes, weight gain (22.5–27.0 kg), and diarrhea that had occurred over the prior several months. In the month leading up to her recent admission, she developed anasarca and had suffered a nontraumatic fracture of the right hip. On physical exam, she was hypertensive despite the multiple antihypertensive medications (losartan, clonidine, amlodipine, and ramipril) that had been prescribed to her by various physicians during her numerous hospitalizations. She had moon facies, facial plethora, supraclavicular fullness, and a dorsal fat pad. A diffuse maculopapular rash was present on her face and upper extremities. She had diffuse anasarca and her abdomen was centrally obese and firm with thick, purple, abdominal striae and multiple ecchymoses.

Our initial laboratory results indicated hypokalemia, hyperglycemia, and metabolic alkalosis. She had a potassium level of 3.1 mEq/L (3.6–4.8 mEq/L) and a glucose level of 134 mg/dL (70–100 mg/dL). Arterial blood gas testing showed a pH of 7.55 (7.35–7.45), PaCO₂ of 36.9 mm Hg (35–45 mm Hg), PaO₂ of 72.2 mm Hg (80–100 mm Hg), and bicarbonate of 32.3 mEq/L (22–26 mEq/L). Blood urea nitrogen and creatinine levels were normal. An accurate glomerular filtration rate could not be calculated because of her anasarca. Complete blood cell count was within normal limits.

Fig. 1. Diagnostic algorithm for suspected Cushing's syndrome. ACTH-independent sources adrenocortical adenoma, adrenocortical carcinoma, and bilateral micronodular dysplasia; **ACTH-dependent sources** pituitary hypersecretion of ACTH, ectopic ACTH-secreting tumors, and CRH-secreting tumors. The *plus/minus* symbol indicates that it is evaluated with pituitary MRI and possible petrosal venous sampling.

Clinical history and exam suggested Cushing's syndrome which was confirmed with a 24-hour urine collection of 4,175 mL that contained 5,219 µg/24 h of cortisol (reference range, 3.5–45 µg/24 h), greater than 4 times the upper limit of normal. Her serum cortisol level was 39.5 µg/dL (5–25 µg/dL), and plasma ACTH was 133 pg/mL (10–60 pg/mL) consistent with an ACTH-dependent source. Our pathologist's review of her outside pathology slides confirmed carcinoid (chromogranin, synaptophysin, and pankeratin positive; CEA negative), therefore, identifying an ectopic source. We did not pursue further testing with dexamethasone suppression or CRH stimulation tests. Baseline serum 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A, markers of carcinoid, were elevated; 9.9 mg (0.0 mg–6.0 mg) and 1,300 ng/mL (0.0 ng/mL–225 ng/mL), respectively.

Computed tomography (CT) of the abdomen and pelvis revealed at least 12 hyperdense lesions located diffusely within the liver that were consistent with metastatic tumor. The largest liver lesion measure 3.6 cm in diameter. No other lesions were identified in the abdomen or pelvis. The adrenal glands were hyperplastic but without evidence of adenoma. We searched for pulmonary lesions with a high-resolution CT scan of the chest which was negative. Magnetic resonance imaging of the brain with dynamic contrast imaging of the pituitary was

normal. A whole-body scan using indium In-111 pentetreotide, a diagnostic radiopharmaceutical (OctreoScan; Tyco Healthcare, Mansfield, MA, USA), showed areas of increased uptake throughout the liver but no other regions of uptake. Inferior petrosal sinus sampling was not undertaken because an ectopic source for the patient's Cushing's syndrome had already been established. Upper and lower endoscopies were completed and were also negative for gastrointestinal lesions. Bone scans were completed and were negative for bony metastasis. The primary carcinoid tumor has not been identified despite periodic restaging with repeat CT scans of the chest, abdomen, and pelvis as well as repeat bone scans.

Treatment with octreotide was started, and the patient underwent bilateral adrenalectomy with appropriate endocrine replacement therapy. To date, she continues to receive monthly octreotide injections and is currently receiving sorafenib in a clinical trial. The patient has had a dramatic improvement in her quality of life since her adrenalectomy. Her hyperglycemia and hypertension are both well-controlled. Although hypercortisolism resulted in multiple vertebral compression fractures, vertebroplasty has provided considerable pain relief. Since her treatment began, the patient has lost 21.3 kg, her strength has improved, and she has felt well enough to travel extensively.

DISCUSSION

Cushing's syndrome often presents a diagnostic challenge, particularly in the early stages when the signs and symptoms are nonspecific. Obesity, hypertension, and glucose intolerance are just a few of the early clues that unfortunately are also very prevalent in our society. The classic description of proximal muscle weakness, wide purple abdominal striae, and increased supraclavicular fat occurs in only a minority of patients.¹ Although considered a classic finding of Cushing's syndrome, central obesity with limb wasting is a feature of long-standing cortisol excess and, therefore, is a late finding. In 1 study of 70 patients clinically suspected to have Cushing's syndrome, discriminatory indices were assigned to symptoms based on their prevalence in patients proven to have Cushing's syndrome versus those who did not. Three clinical features; ecchymoses, myopathy, and hypertension, were found to have the highest discriminatory value for Cushing's disease in those studied.²

Adding to the clinical dilemma are the serious consequences of unrecognized hypercortisolism. A National Institutes of Health study found that hypercortisolism conferred a heightened risk of both infection and pulmonary embolism.³ The hypertension, hypercoagulability, and metabolic syndrome that result from hypercortisolism increase cardiovascular risk, the main cause of increased mortality in this patient population.^{1,4,5} Pathologic fractures are also common, occurring in 30–50% of Cushing's patients.⁵ A high index of suspicion is necessary for patients with clinical features suggestive of cortisol excess. Based on our review of the literature, we developed an algorithm to help guide the evaluation of Cushing's syndrome (Fig. 1). Because Cushing's syndrome was suspected after a carcinoid lesion was already identified, our workup varied somewhat from this algorithm.

A 24-hour urine-free cortisol level that is more than 4 times the upper limit of normal is diagnostic for Cushing's syndrome. Levels between 1 and 4 times the normal require further testing for definitive diagnosis. An elevated midnight salivary cortisol result can aid in this confirmation; however, the diagnostic criteria of this test need further validation.¹ Definitive diagnosis can be achieved by a 2-day dexamethasone stimulation (0.5 mg every 6 hours for 2 days) combined with corticotropin-releasing hormone (CRH) (1 mg given 2 hours after the last dexamethasone dose). A plasma cortisol level of 1.4 µg/dL or higher is positive for Cushing's syndrome with almost 100% sensitivity and specificity.⁶ Alternatively, the diagnosis of Cushing's syndrome is achieved when a 1-mg overnight dexamethasone suppression test results in an 8 A.M. serum cortisol level higher than 14.3 µg/dL. This test has limited utility, however, because total suppression of cortisol does not rule out Cushing's syndrome.¹

Plasma ACTH levels distinguish ACTH-dependent from ACTH-independent causes of Cushing's syndrome. A plasma ACTH level lower than 5 pg/mL with a serum cortisol level higher than 15 µg/dL indicates an ACTH-independent source. ACTH-independent sources are primary to the adrenal glands and include adrenocortical adenomas and carcinomas and, less often, bilateral micronodular dysplasia. A plasma ACTH level higher than 10 pg/mL despite a serum cortisol level higher than 15 µg/dL indicates an ACTH-dependent cause. ACTH-dependent sources include pituitary hypersecretion of ACTH (Cushing's disease), ectopic ACTH-secreting tumors, and ectopic CRH-secreting tumors.^{1,7}

Intermediate ACTH levels are indeterminate and require further evaluation, which can be accomplished using a CRH stimulation test. This test is also useful in differentiating pituitary from ectopic ACTH secretion in known ACTH-dependent Cushing's syndrome.^{1,8} After baseline ACTH and cortisol levels are measured, 1 µg/kg (alternatively, 100 µg) of CRH is administered. Levels of ACTH are measured at 15 and 30 minutes and cortisol at 30 and 45 minutes after administration. A 35% rise in ACTH and a 20% rise in cortisol together have a 90% sensitivity and specificity for a pituitary source of excess ACTH.⁸

Another method to distinguish a pituitary source from an ectopic source is an overnight 8-mg dexamethasone suppression test. High-dose dexamethasone overcomes feedback inhibition in pituitary tumors but does not in ectopic tumors. A greater than 68% suppression of serum cortisol offers 71% specificity and 100% sensitivity in identifying a pituitary source for ACTH-dependent Cushing's syndrome.⁸ Ectopic ACTH-secreting tumors include carcinomas of the lung, thymus, and pancreas, as well as carcinoid tumors. Secretion of ACTH results in bilateral adrenocortical hyperplasia, adrenal hyperfunction, and resultant Cushing's syndrome.^{9,10} Our case illustrates an unusual case of Cushing's syndrome secondary to adrenal hyperplasia caused by carcinoid.

Carcinoid is an extremely rare neuroendocrine tumor with an incidence in the United States of 1 to 2 cases per 100,000 people.¹¹ Although classically associated with carcinoid syndrome (paroxysmal diarrhea, flushing, and hypertension), carcinoid tumors are often asymptomatic and discovered incidentally during unrelated surgery or imaging.^{9,11} The location and likely presentation of a carcinoid tumor depends on the division of the embryonic gut from which the tumor cells originate. Carcinoid tumors originating from foregut cells arise in the lungs, bronchi, and stomach and, when symptomatic, are likely to cause recurrent pneumonia, cough, anemia, or abdominal pain. Hindgut derivatives arise in the distal colon and rectum and are likely to cause pain, bleeding, and constipation. It is the midgut tumors, which are found in the small intestine, appendix, and proximal large bowel, that are most commonly associated with carcinoid syndrome.⁹

Derived from neuroendocrine cells, carcinoid tumors have the ability to secrete various peptides and bioactive amines. The most commonly secreted substance is the bioactive amine serotonin (5-hydroxytryptamine), the amine responsible for the classic manifestations of carcinoid syndrome (paroxysmal diarrhea, flushing, and hypertension).¹¹ Bioactive amines such as serotonin and histamine are cleared by the liver, explaining why carcinoid syndrome is unlikely unless liver metastases have occurred.^{9,11} When it does occur, carcinoid syndrome is seen with midgut-derived carcinoid tumors that have metastasized to the liver (although rarely it may be seen with any serotonin-secreting carcinoid that drains directly into the systemic circulation).⁹

As uncommon as the presentation of classic carcinoid syndrome may be, a far less common presentation is that of Cushing's syndrome because of ectopic ACTH production. Although serotonin is the most common substance secreted by carcinoid tumors, a number of peptides are possible, including ACTH.¹¹ Excess ACTH results in hypercortisolism, which in turn causes both Cushing's syndrome and hypokalemia. The degree of hypokalemia is directly related to the amount of urine-free cortisol.⁸ Cushing's syndrome results from a nonpituitary tumor, such as carcinoid, in somewhere

between 10% and 20% of cases.^{1,3,8} When Cushing's syndrome is caused by ACTH-secreting carcinoid tumors they are most often bronchial or thymic in origin, although cases of gastrointestinal carcinoids have been reported. Primary carcinoid lesions are either occult or unlocalized in up to 20% of cases.^{3,12,13} Rare cases of primary liver carcinoid tumors have been reported; however, fewer than 80 cases exist in the literature, only 1 of which has been reported as an ectopic source of ACTH production.¹⁴

Definitive treatment of carcinoid involves surgical resection of the primary lesion. In the case of ACTH-producing carcinoid tumors, this will induce both remission of symptoms and return of normal adrenal function.¹ As in our patient, when the primary lesion cannot be localized, treatment rests with medical or surgical attempts to control the symptoms of both carcinoid and Cushing's syndromes. The somatostatin analog octreotide is currently the mainstay of treatment for carcinoid symptoms. Octreotide works by preferentially binding to the sst2 somatostatin receptor and inhibiting secretion of the peptides and amines (5-hydroxytryptamine and tachykinins) commonly released by carcinoid tumors. Octreotide reduces the symptoms of diarrhea and flushing and is thought to have a concentration-dependent effect on tumor suppression.¹⁵ For resectable lesions, if preoperative evaluation determines that at least 90% of the gross tumor is treatable, hepatic resection offers an alternative that may increase 5-year survival and decrease the requirement for somatostatin analog treatment. Hepatic resection is by no means curative and high recurrence rates are reported.^{16,17} Unfortunately, hepatic resection was not an option for our patient because of the number and diffuse location of liver lesions. Finally, alternative treatment options, such as cryoablation, percutaneous alcohol injection, and radiofrequency ablation, exist; however, data regarding their use in neuroendocrine liver metastases are limited.¹⁸

When ACTH secretion results in Cushing's syndrome, immediate control of hypercortisolism is required to reduce morbidity and mortality. This was illustrated by a large retrospective case study that found patients with occult ACTH-secreting tumors had a good prognosis, despite failure to localize their tumor, if adequate control of hypercortisolism was achieved.³ Adrenolytic medications such as ketoconazole may have a role in suppressing cortisol levels; however, they are often less successful in these patients because of the amount of adrenal stimulation observed.¹³ Bilateral adrenalectomy continues to be an effective measure to eliminate severe hypercortisolism in these patients.^{12,19,20} Immediate bilateral adrenalectomy was indicated for our patient because of life-threatening hypertensive crisis, intractable diarrhea, and severe debilitation. Bilateral adrenalectomy combined with octreotide resulted in a dramatic reduction of symptoms and improvement in overall quality of life. Serum 5-HIAA levels have returned to within normal limits and chromogranin A levels have decreased dramatically.

CONCLUSION

Early recognition of the signs and symptoms of ectopic ACTH is needed for prompt and adequate intervention. Based on our review of the literature, we developed an algorithm that can guide the evaluation of Cushing's syndrome (Fig. 1). Treatment for carcinoid tumors with ectopic ACTH secretion involves

surgery and administration of octreotide. Hypercortisolism can sometimes be treated temporarily with ketoconazole or other medication, but bilateral adrenalectomy is often mandated. Surgery combined with octreotide resulted in a dramatic reduction of symptoms and improvement in overall quality of life for our patient.

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