

A Woman with Long-Standing Hypertension Diagnosed with Metastatic Adrenal Carcinoma

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ABSTRACT

Adrenocortical carcinomas are rare tumors with varied presentation. In this case report we present a 64-year-old woman with a history of poorly controlled hypertension who subsequently developed Cushingoid features, hirsutism, hypokalemia, hypercortisolemia, increased serum testosterone levels, and diabetes mellitus. At time of diagnosis, she was found to have a metastatic adrenocortical carcinoma. Survival with adrenocortical carcinoma is poor and considerable uncertainty remains as to the optimal approach for treatment when this tumor type is either still confined to the adrenal gland or when it becomes metastatic.

INTRODUCTION

Adrenocortical carcinomas (ACCs) are rare malignancies characterized by a poor prognosis.¹ The incidence is

approximately 0.5-2 cases per million population per year. Sixty percent of ACCs are secretory. Adults with hormone-secreting ACCs usually present with Cushing's syndrome alone (45%), or a mixed Cushing's and virilizing syndrome with overproduction of both glucocorticoids and androgens (25%). Fewer than 10% percent present with virilization alone, but the presence of virilization in a patient with an adrenal neoplasm suggests an ACC rather than an adenoma. Feminization and hyperaldosteronism occur in fewer than 10% of cases.¹

Most patients with nonfunctioning tumors present with clinical manifestations related to tumor growth (ie, abdominal or flank pain), or with an incidentally found adrenal mass detected on radiographic imaging performed for a different reason. The diagnosis of ACC involves taking a careful clinical history and performing a physical examination and diagnostic, radiologic, and laboratory testing to exclude pheochromocytoma, hyperaldosteronism, hyperandrogenism, and Cushing's syndrome (often presenting with hypertension, diabetes, virilization, and hypokalemia).

Table 1. Biochemical Markers in a 64-Year-Old Woman with Metastatic Adrenal Carcinoma

Laboratory Measure	Patient Value	Established Normal Values
Potassium	2.1	3.5-5.1 mmol/L
Aldosterone	7 (supine)	3-16 ng/dL
Cortisol	80.4 (7-9 am)	4-22 µg/dL
Testosterone	136	20-75 ng/dL

In this case report, a woman with a long standing history of hypertension was admitted to the hospital with hirsutism, severe hypokalemia, and metabolic alkalosis prompting endocrine evaluation and imaging studies which led to the diagnosis of metastatic ACC. She had been under medical treatment for hypertension for over 2 decades. These significant findings during the course of her illness can prompt earlier evaluation in patients with similar signs and symptoms.

Case Report

A 64-year-old white female presented with uncontrolled hypertension, diabetes mellitus, hypokalemia, metabolic alkalosis, and abdominal pain. She was initially diagnosed as having hypertension at the age of 44 years. Her physician at that time found her hypertension to be labile and evaluated her 24-hr urinary catecholamine and vanillylmandelic acid (VMA) levels in March 1986, which were normal. She was initially treated with a thiazide diuretic and a beta blocker. She subsequently established care with another physician who added a calcium channel blocker to improve blood pressure control. Urinary catecholamines were evaluated again in 1997 and 2003 and were found to be normal. Renal ultrasonography in November 2003 revealed the presence of multiple small left-sided renal cysts. No adrenal or renal masses were noted on either side.

In response to continued difficulty

controlling her blood pressure, minoxidil was added to her antihypertensive regimen in February 2005. She developed hirsutism that was assumed to be secondary to minoxidil-induced hypertrichosis. She had persistent hypokalemia that was thought to be induced by diuretic therapy and she was placed on increasing doses of potassium supplementation. One month later she developed new onset diabetes mellitus. She was admitted to the hospital in April 2005 with hypoglycemic coma. At that time she presented with Cushingoid features and a metabolic alkalosis with pH 7.61, pCO₂ 40 mEq/L, and a bicarbonate level of 40 mEq/L.

Cortisol and aldosterone levels were measured. Her pertinent laboratory results are given in Table 1. Computed tomography revealed a left adrenal mass measuring 9.5 x 5.5 cm with irregular areas of contrast enhancement suggestive of necrosis. There were also liver and lung nodules suggestive of metastatic disease (Figure 1). A needle biopsy of the liver nodule was planned but she subsequently developed an acute abdomen secondary to diverticular perforation, necessitating emergency laparotomy. A large left adrenal tumor was found with multiple liver nodules. Biopsy of the liver lesion showed a solid, small cell tumor with a trabecular pattern (Figure 2). Immunohistochemical staining of the tumor showed positive reactivity with inhibin, melan-A, and synaptophysin, supporting the diagnosis of metastatic ACC (Figure 3). Chromogranin was negative, ruling out

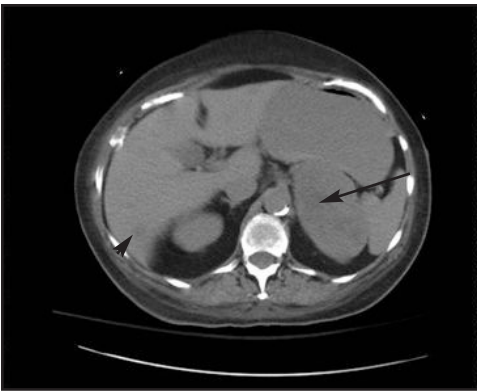


Figure 1. Abdominal computed tomography scan of a 64-year-old woman who presented with uncontrolled hypertension, diabetes mellitus, hypokalemia, metabolic alkalosis, and abdominal pain. The large arrow indicates a large adrenal mass measuring 9.5 x 5.5 cm. The arrowhead points to liver metastasis.

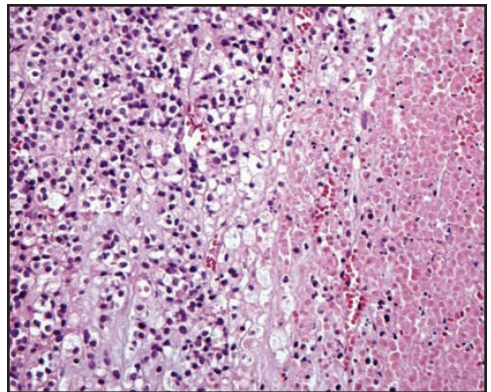


Figure 2. Small wedge biopsy of liver in this patient showed total replacement of liver architecture by small tumor cells with clear cytoplasm (left) and large areas of adjacent necrosis (right). (200x magnification, hematoxylin and eosin stain)

pheochromocytoma. Epithelial membrane antigen, proximal nephrogenic renal antigen (PNRA), and CAM5.2/AE1 were negative, excluding a renal origin for the tumor.

The patient experienced a complicated post-operative course, developed adult respiratory distress syndrome, and expired on the 11th postoperative day.

DISCUSSION

Based on a series of 22 patients, the most common finding in ACC is poorly controlled hypertension, even when treated with multiple antihypertensive agents.² This patient had uncontrolled hypertension that prompted repeated endocrine evaluation over the course of nearly 20 years. The clinical focus was on the exclusion of a pheochromocytoma alone. It was only in the terminal part of her illness that a secreting adrenal tumor other than pheochromocytoma was suspected. She was found to have a cortisol- and androgen-producing ACC which was already metastatic. Since ACC has a poor prognosis, it is unlikely that she was afflicted with this tumor for an extended period of time. However, there were clues in her clinical course

that could have prompted earlier evaluation and diagnosis.

The development of hirsutism was assumed to be secondary to minoxidil-induced hypertrichosis. Hirsutism is the presence of an increase in androgen-dependent terminal hair on the lip, chin, chest, abdomen, and back, areas where there are few or no hairs in normal women. Hypertrichosis describes the excessive growth of androgen-independent hair prominent in non-sexual areas, and is most commonly caused by systemic disorders or medications like minoxidil. This underscores the importance of elicitation and interpretation of clinical signs. In a suspected case of adrenal neoplasm, or in elucidating the cause of secondary hypertension in addition to excluding pheochromocytoma by serum metanephrine or VMA in urine, cortisol production should also be measured by either serum cortisol levels or a low-dose dexamethasone suppression test. This is recommended by the National Institutes of Health Consensus Panel.³

The clinical diagnosis, pathology, and management of ACC has been extensively reviewed recently.⁴ ACC is a

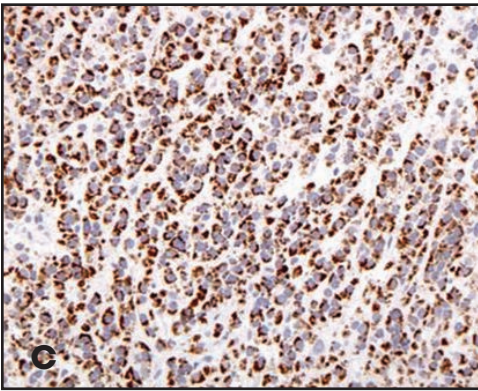
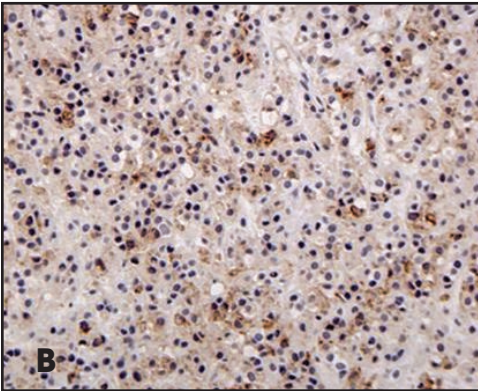
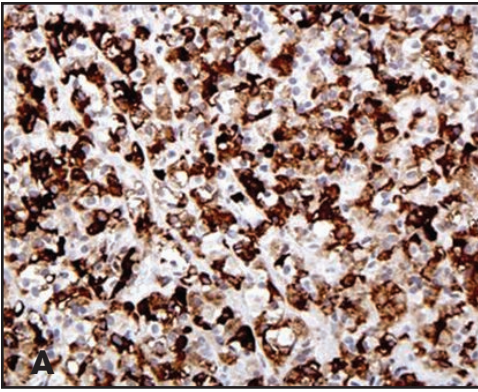


Figure 3. Immunohistochemical staining of the tumor showed positive reactivity with (A) inhibin, (B) synaptophysin, and (C) melan-A.

rare disease with a worldwide incidence of 0.5-2 cases per million people annually.⁵ There is a bimodal distribution with a small peak in children younger than 5 years of age and another peak in adults in their fourth and fifth decades. A slight-

ly higher incidence is reported in females. The most common presentation is that of Cushing's syndrome. The overproduction of androgens may go unnoticed in males; however, in females it causes hirsutism, menstrual irregularities, male pattern baldness, and a deepened voice. True overproduction of aldosterone, which is less common, presents with hypertension and hypokalemia.

Whenever an adrenal tumor is suspected, appropriate biochemical analysis is directed toward the detection of excess cortisol, androgens, aldosterone, and catecholamines. A cortisol excess can be confirmed by elevated free cortisol levels in a 24-hr urine specimen or elevated plasma free cortisol. An overnight low-dose dexamethasone suppression test is more sensitive than the measurement of free cortisol levels. The measurement of 17-ketosteroids in a 24-hr urine specimen is the initial test of choice for the detection of an androgen or estrogen excess. Further testing may include serum dehydroepiandrosterone (DHEA) and its derivatives. When a patient presents with hypertension and hypokalemia in the context of a high index of suspicion for adrenal dysfunction, a serum aldosterone level should also be measured. All patients with an adrenal tumor should be assessed for pheochromocytoma. The simplest and most reliable test for evaluating pheochromocytoma is measurement of plasma free metanephrines rather than traditional testing by quantitating urinary vanillylmandelic acid or catecholamines.

Computed tomography (CT) scanning remains the initial imaging modality of choice for the diagnosis and characterization of adrenal tumors. On nonenhanced images, ACCs have attenuation values >30 Hounsfield units (HU) as do other malignant tumors such as metastases or pheochromocytomas. Benign tumors have attenuation values

≤10 HU. On contrast enhanced CT images, ACCs appear as heterogenous with occasional calcifications and have irregular borders. Magnetic resonance imaging (MRI) better differentiates between benign and malignant tumors and demonstrates invasion into surrounding structures, particularly the inferior vena cava. The National Institutes of Health consensus criteria³ recommends that any adrenal mass above 6 cm be resected, regardless of its functional status or imaging characteristics; however, size alone should not be considered as the defining criterion with which to distinguish benign versus malignant lesions, as both small ACCs and large adenomas can occur frequently. Heterogenous tissue attenuation on CT scanning or heterogenous signal intensity on T₂-weighted MRI images are helpful indicators of malignancy, irrespective of the size of the adrenal mass.⁶

Adrenocortical carcinomas account for 14% of all incidentalomas. Single institution and cooperative group studies suggest early diagnosis is associated with improved outcomes; however, this does not seem to be true from the largest cohort study of 725 cases analyzed from SEER data (1973 to 2000).⁷

The only potentially curative treatment for ACC is surgery. However, only 35% of these tumors are resectable at the time of diagnosis.⁸ Maximal debulking is advocated by some surgeons as a means of improving survival in unresectable tumors,⁹ although some disagree.¹⁰ Untreated, patients with unresectable disease survive only 3-9 months.¹

Because of the rarity of the disease there are no evidence-based choices in the management of ACC. Various chemotherapeutic agents have been used either alone or in combination with mitotane. Mitotane, a congener of the insecticide DDT, an adrenocorticolytic

drug, has some efficacy in patients with ACC. The main benefit is a reduction in symptoms. Response seems to be related to maintaining serum mitotane levels above 10 µg/mL. The typical dosage is 2-5 g daily. Administration of mitotane is complicated by numerous adverse side effects. Hormonal responses are reported in up to 75% of patients, and tumor size is reduced in as many as one-third of cases.¹¹

Experience with chemotherapeutic agents is limited. The largest series included 72 patients who received monthly doses of etoposide, doxorubicin, and cisplatin as well as oral mitotane up to 4 g daily. A complete response was achieved in 5 patients and a partial response in 30. A complete hormone response was noted in 9 of 16 patients with functional tumors. The average time to progression in responding patients was 24 months. The addition of mitotane increased neurologic and gastrointestinal side effects.¹² Intensive multi-modality treatment with allogeneic stem cell transplantation has been recently reported in a case report with a survival of 39 months.¹³

SUMMARY

In summary, ACC is a rare tumor with very poor prognosis. The most important and consistently observed determinants of improved survival are localized tumors, complete surgical resection, and tumor grade. In cases of persistently uncontrolled hypertension, a thorough endocrine work-up should be instituted including imaging studies to diagnose early adrenal tumors. The case described herein illustrates the importance of accurate elicitation and interpretation of clinical signs. It also illustrates a point that iatrogenic side effects of medications should not be confused with de novo signs of a pathological condition. Since hypertension is the most common presenting feature of ACC, it cannot be

overemphasized that suspected cases undergo thorough evaluation to improve on resectability rates in ACC, which is currently dismal in the reported literature.⁸

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