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Guess the Case from the Ochsner Clinic

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INTRODUCTION

A 63-year-old man complaining of painless hematuria was seen by his primary care physician. Prostatitis was diagnosed by history and urinalysis. A computed tomographic (CT) scan revealed a left adrenal mass measuring 3.8 cm in diameter (see Figure 1). No evidence of nephrolithiasis was seen, and he was referred to the Endocrinology Department for evaluation of the adrenal mass.

His medical history is significant for hypertension, coronary artery disease requiring stenting, carotid artery stenosis requiring angioplasty, and dyslipidemia. His surgical history includes a neck exploration after trauma, tonsillectomy, adenoidectomy, hemorrhoidectomy, and cataract surgery. He is a smoker and drinks alcohol occasionally. His father had a brain tumor and his mother had dementia, heart disease, and diabetes. He denied any family history of pituitary or adrenal disorders.

His medications include clopidogrel, aspirin, simvastatin, atenolol, and valsartan. He denied vision changes, headaches, chest or abdominal pain, diaphoresis, polyuria, nocturia, paresthesias, or erectile dysfunction. He had no history of depression or fractures.

His blood pressure was 165/80 mm Hg with a pulse of 70 beats per minute. Physical examination revealed an obese (229 lb, 71 in, body mass index = 30) man. There were no abdominal striae, moon facies, or supraclavicular fullness, and no skin abnormalities or bruising. The remainder of his physical examination was unremarkable.

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Upon review of his past laboratory studies, fasting hyperglycemia (118–165 mg/dL) was noted. A biochemical work-up (Table 1) was significant for abnormal 1 mg dexamethasone suppression, elevated urinary cortisol, and low adrenocorticotropic hormone (ACTH). A repeat 24-hr urine cortisol level remained elevated at 87 μg/24 h. Bone mineral density was normal.

WHAT IS THE DIAGNOSIS?

Subclinical Cushing's syndrome (SCCS) was diagnosed because of the presence of an adrenal mass with abnormal 24-hr urinary-free cortisol, abnormal dexamethasone suppression, and comorbid hypertension, hyperglycemia, obesity, and cerebrovascular and coronary artery disease. A surgical consultation was obtained.

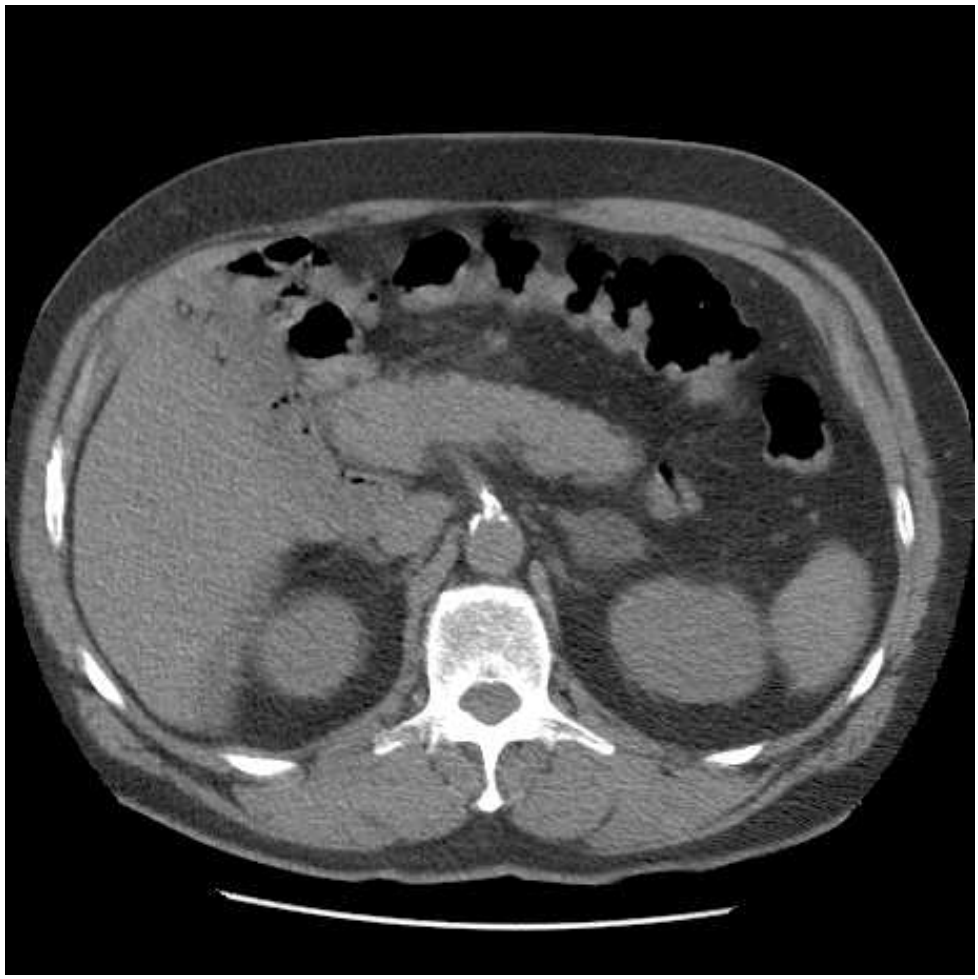
The patient underwent a laparoscopic left adrenalectomy using an anterolateral transabdominal approach without complication. Perioperative steroids were not administered. His postoperative course was unremarkable, and he was discharged to home on postoperative day 1. Pathological analysis showed a 6-cm benign cortical adenoma.

Postoperative laboratory studies showed normal 1 mg overnight dexamethasone suppression (1.2 μg/dL), resolution of his urinary hypercortisolism (43 μg/24 h) as well as normalization of his ACTH level (16 pg/mL). At 3-month follow-up, he has lost 5 pounds and has normal fasting blood glucose levels. His blood pressure has decreased to 130/65 mm Hg without medication changes.

DISCUSSION

Most adrenal masses, as in our patient, are discovered incidentally in the course of imaging obtained for evaluation of non-adrenal pathology. These ''incidentalomas'' are seen with increasing frequency as the role of cross-sectional imaging expands and may be present in 2%–9% of individuals (as suggested by autopsy studies) (1). The prevalence of biochemically active incidentalomas is difficult to ascertain because of differences among thresholds used in screening tests for biochemical function. Recent studies using lower cutoff levels for dexamethasone suppression (<1.8 μg/dL) suggest that the majority of incidentalomas secrete cortisol (2,3).

Figure 1. Non-contrast CT demonstrating left adrenal mass.



Overt (clinically apparent) Cushing's *syndrome* refers to hypercortisolism from any source, whereas Cushing's *disease* denotes ACTH-dependent hypercortisolism (usually from a pituitary tumor). Clinical findings in Cushing's syndrome are listed in Table 2 (4,5). Overt Cushing's syndrome is rare, with an estimated incidence of 1:500,000 (4). Approximately 20% of cases of Cushing's syndrome have an adrenal etiology, with the majority of cases of Cushing's syndrome being attributable to pituitary microadenoma.

Table 1. Initial biochemical data.

	Lab value	Normal
Glucose	138	70–110 mg/dL
1 mg dexamethasone suppression	2.2	<1.8 μg/dL
24-hr urine free cortisol	60	3.5–45 μg/24 h
Random cortisol	15.1	3.1–22.4 μg/dL
ACTH	<5.0	10–60 pg/mL
Potassium	3.8	3.3–5.3 mg/dL
Plasma renin activity	0.9	0.6–3.0 ng/mL/h
Aldosterone	3.6	1–21 ng/dL
Norepinephrine	617	70–750 pg/mL
Epinephrine	34	0–110 pg/mL
Dopamine	18	0–29 pg/mL

ACTH=adrenocorticotropic hormone

SCCS is a heterogeneous condition and is marked by a spectrum of clinical and biochemical findings (see Table 3) (4,6). We define SCCS as partially ACTH-independent hypercortisolism without the physical findings usually associated with overt Cushing's syndrome (see Table 2). SCCS is biochemically diagnosed by having at least two abnormal tests: an abnormal dexamethasone suppression test, an ACTH level below 15 pg/mL, and/or a high urinary-free cortisol.

A diagnostic evaluation of an incidentally discovered adrenal mass should focus on a determination of the risk for malignancy and a search for evidence of biochemical function. This requires a thorough history and physical examination, cross-sectional imaging of high quality, and a battery of endocrine function tests

Table 2. Signs and symptoms of hypercortisolism.

- Plethora
- Moon face
- Buffalo hump
- Central (truncal) obesity
- Easy bruising
- Deep purple striae
- Proximal muscle weakness
- Menstrual irregularities
- Acne
- Hirsutism
- Osteoporosis
- Depression
- Glucose intolerance or diabetes mellitus
- Systolic or diastolic hypertension
- Low high density lipoprotein (HDL)
- Elevated triglycerides
- Increased fibrinogen
- Accelerated atherosclerosis

(see Table 4) (7) to determine the presence or absence of hypercortisolism, pheochromocytoma, and hyperaldosteronism.

Adrenal malignancy is extremely rare, but more likely in adrenal masses that are large (>4–5 cm), of higher density (lower fat content), irregularly bordered, or invasive to contiguous structures. The adrenal gland may be the target of metastases from remote sites, most commonly lung and breast.

A diagnosis of SCCS should be considered in those patients with adrenal masses who do not display classic ''Cushingoid'' features and in whom endocrine tests of cortisol function are abnormal (i.e., elevated 24-hr urinary free cortisol, abnormal dexamethasone suppression, low plasma ACTH). Patients with SCCS who have comorbidities that could be

Table 3. Biochemical abnormalities found in subclinical Cushing's syndrome (4)*.

- Elevated urinary-free cortisol
- Low or suppressed plasma ACTH
- Missing cortisol suppression after standard low-dose dexamethasone suppression test
- Missing cortisol suppression after 1-mg overnight dexamethasone suppression test
- Missing cortisol suppression after high-dose dexamethasone suppression test
- Blunted diurnal variation of cortisol secretion
- Low dehydroepiandrosterone sulfate concentrations
- A blunted response of ACTH to stimulation with corticotropin-releasing hormone

* Information extracted from Reincke M. Endocrinol Metab Clin North Am 2000; 29:43–56.

Table 4. Biochemical tests useful in the evaluation of an incidentaloma (4,7)*.

- 24-hour urinary-free cortisol
- 1-mg overnight dexamethasone suppression test
- Plasma ACTH level
- Fractionated plasma metanephrines
- 24-hour urinary catecholamines
- Plasma aldosterone concentration
- Serum potassium level
- Plasma renin activity

* Information extracted from Reincke M. Endocrinol Metab Clin North Am 2000; 29:43–56 and from Young WF Jr. N Eng J Med 2007; 356:601–610.

exacerbated by persistent hypercortisolism are candidates for adrenalectomy.

Adrenalectomy is recommended for larger adrenal masses (typically >4–5 cm), masses which have grown in size, those with hormonal overactivity (including SCCS), and those suspicious of malignancy (4,8–11). Laparoscopic adrenalectomy has proven equally efficacious to open adrenalectomy with regard to cure for functioning adrenal masses. In addition, a laparoscopic approach is superior with regard to pain, length of hospitalization, and postoperative complication rates. Relative contraindications to laparoscopic adrenalectomy are tumor invasion to surrounding structures or metastatic lymph node involvement. Perioperative steroids should be considered, especially with evidence of decompensation or contralateral adrenal atrophy (8).

In our patient, normalization of the pituitary-adrenal axis was demonstrated postoperatively, as well as a trend toward weight loss and improvement in hypertension and hyperglycemia. Similar findings have been reported elsewhere (6). Does this predict a decrease in his morbidity and mortality? At present, the question of whether surgical removal of adrenal incidentalomas associated with SCCS affects comorbidities associated with hypercortisolism is unresolved. This is, in part, due to the variability in defining SCCS among institutions. No biochemical or clinical gold standard exists for the diagnosis of SCCS (12). In addition, the relatively high prevalence of components of the metabolic syndrome in the face of a low incidence of SCCS (by any definition) makes proving a causal relationship difficult. An association between SCCS and increasing cardiovascular risk (by surrogate markers) has been suggested (13); however, the question of whether SCCS portends an increased morbidity and mortality as seen in overt Cushing's syndrome remains unanswered.

The classic teaching is that an adrenal adenoma that causes Cushing's syndrome is ACTH-independent. In our patient, laparoscopic removal of the

adrenal gland corrected all of the abnormal tests of cortisol function (ACTH level, urinary free cortisol and 1-mg dexamethasone suppression). Thus, the enlarged adrenal gland was responsible for the excess cortisol secretion.

There are some atypical aspects to this case. First, the random cortisol of 15 μg/dL declined to 2.2 μg/dL after dexamethasone suppression, suggesting that there was some degree of ACTH dependency. Second, the current recommendations for adrenalectomy use a cortisol level of 5.0 μg/dL after 1-mg dexamethasone suppression. Recent studies suggest that normal suppression post-dexamethasone should be less than 1.8 μg/dL (2,3). Third, the patient did not need glucocorticoid replacement postoperatively. Our interpretation is that the patient had excess cortisol secretion, but that it was, in part, ACTH-dependent and that the contralateral normal adrenal was still functioning.

We suggest that there is a spectrum of adrenal disease from ACTH-dependent to ACTH-independent hypercortisolism. Subclinical Cushing's with an adrenal incidentaloma is more likely to be associated with a degree of ACTH-dependency, and overt Cushing's syndrome is more likely to be associated with ACTH-independence. Further studies are needed to test this hypothesis. In addition, we suspect that the postoperative adrenalectomy requirements for glucocorticoid replacement should be less for SCCS than for overt Cushing's syndrome, owing to the lesser degree of hypercortisolism seen in SCCS.

A study of clinical and biochemical characteristics and cardiovascular risk outcomes in patients with SCCS treated with laparoscopic adrenalectomy is currently underway at Ochsner Clinic Foundation.

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