Diagnosing a Unilateral Cortisol-Producing Adrenal Adenoma in a Patient on Exogenous Glucocorticoids

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Cushing syndrome due to the administration of pharmacologic doses of glucocorticoids is common, whereas hypercortisolism from an adrenal mass is quite rare. Adrenal masses are incidentally detected with a prevalence ranging from 8.7–12.4%,[1] and most of these lesions are hormonally inactive.[2] In this article, we describe a unique patient with a glucocorticoid-producing adrenal mass who was diagnosed while on exogenous glucocorticoid therapy.

CASE REPORT

A 51-year-old woman with type 2 diabetes mellitus diagnosed in 1986, hypertension, hyperlipidemia and long-standing amenorrhea was well until May 1990 when she developed a large ulcer in the proximal lateral aspect of her right lower leg. Two separate biopsies were negative for vasculitis and offered no definitive diagnosis. Lower extremity ultrasound showed normal arterial flow and no venous thrombosis.

In February 1991 our patient was found to have nephrotic range proteinuria (5.6g/24 hours) with normal urine sediment. In April 1991, she was treated empirically for livedoid vasculitis and unexplained nephrotic syndrome with oral prednisone (60mg daily for 2 weeks tapered to 20–40 mg daily). Complete blood counts, coagulation studies, antinuclear antibodies, creatinine kinase and complement levels were normal. An abdominal MRI, which was done to rule out renal vein thrombosis revealed a 2.5 cm right adrenal mass.

By May 1991 diabetes and hypertension were poorly controlled, her leg ulcer persisted and she developed proximal myopathy and easy bruisability. Cyclophosphamide was started as a steroid-sparing agent, and prednisone was continued at a dose of 30mg once daily. During the subsequent 2 months she underwent debridement and skin grafting of her leg ulcer. Intraoperative biopsies were negative for vasculitis, demonstrating chronic inflammation, phlebitis, myositis and myotrophy.

In July 1991 the patient was transferred to our institution for in-patient rehabilitation, given her severe proximal myopathy. Her present dose of prednisone was 20mg twice a day. Physical examination revealed mild facial plethora, cervicodorsal and supraclavicular fat accumulation, obese abdomen, and proximal muscle weakness, but no striae, hirsutism, or bruising. The right lower extremity skin graft was intact. Albumin and potassium were normal and there was modest proteinuria (422 mg/24 hours). Twenty-four hour urine vanillylmandelic acid, metanephrine and epinephrine were normal.

Cyclophosphamide was discontinued to promote wound healing. To enable accurate evaluation of the hypothalamic-pituitary-adrenal axis, prednisone was replaced with oral dexamethasone 4 mg every 6 hours for 2 days. While on this regimen unsuppressible endogenous cortisol production was demonstrated by a 24-hour urine free cortisol of 524 μg (normal 24–108). The ACTH level was undetectable. Once Cushing syndrome was diagnosed glucocorticoid therapy was discontinued and a repeat ACTH level and 24 hour urine studies performed one month later demonstrated persistent ACTH suppression in the presence of endogenous hypercortisolism. The results are summarized in Table 1.

In anticipation of a unilateral adrenalectomy antiadrenal therapy with ketoconazole (200 mg 5 times daily) was instituted to control hypercortisolism and thereby facilitate wound healing. One month later, 24-hour urine 17-OHCS was 5.1 mg (normal 2–8 mg), free cortisol was 96 μg (normal 24–08) and plasma ACTH level was $<$5 pg/mL (see Table 1). Hyperglycemia and hypertension were then well controlled.

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TABLE 1. Laboratory Data

	Dexamethasone Suppression Test	No Steroids for 1 Month	Antiadrenal Therapy[†]
17-OHCS (mg)[‡]	16.3	11.4	5.1
UFC (μg)[§]	524	285	96
ACTH (pg/mL)[‖]	<5	<5	<5
DHEA-S (μg/dL)[¶]			78

*High-dose dexamethasone suppression with oral dexamethasone 4 mg every 6 h.
[†]Ketoconazole 200 mg 5 times daily for 1 month.
[‡]Twenty-four-hour urine 17-hydroxycorticosteroids (normal 2–8 mg)
[§]Twenty-four-hour urine free cortisol (normal 24–108 mg)
[‖]Adrenocorticotropic hormone (normal 9–52 pg/mL).
[¶]Dehydroepiandrosterone sulfate (normal 82–338 μg/dL).

In December 1991 the patient underwent an uncomplicated open right adrenalectomy. Her pathology revealed a benign adrenal adenoma. She was maintained on low-dose glucocorticoid replacement therapy for a brief period of time postoperatively and followed by her primary care physician.

DISCUSSION

Cushing syndrome is the clinical manifestation of the biologic effects of excessive glucocorticoids on tissues. It is most commonly due to the administration of pharmacologic doses of glucocorticoids. Other causes can be categorized as ACTH-dependent (ie, pituitary adenoma or ectopic secretion of ACTH or CRH) or ACTH-independent (ie, adrenal adenoma or carcinoma).[3] The incidence of classic endogenous Cushing syndrome has been estimated at 1.2–1.7/million year in Denmark, with 22.3% of cases due to benign adrenal adenomas.[4]

The diagnosis of Cushing syndrome relies on the presence of endogenous hypercortisolism and the lack of suppression by dexamethasone.[5] It is essential to first make the definitive diagnosis of endogenous Cushing syndrome before investigating the source of hypercortisolism. Patients in whom Cushing syndrome is suspected are first screened with either an 11 pm salivary cortisol, a 1-mg overnight dexamethasone suppression test, or a 24-hour urinary free cortisol. A 24-hour urinary free cortisol 3-4-fold the upper limit of normal is diagnostic of endogenous Cushing syndrome.[6] Once Cushing syndrome is definitively diagnosed, obtaining a plasma ACTH level can clarify the etiology. An ACTH level <10 pg/mL clearly suggests an ACTH-independent etiology, whereas an ACTH level >20 pg/mL suggest an ACTH-dependent etiology. Intermediate ACTH levels (ie, 10–20) are indeterminate.[5] Determining the precise etiology of ACTH-dependent Cushing syndrome may then require more sophisticated diagnostic tools such as simultaneous inferior petrosal sinus sampling.

In our patient, chronic use of high-dose prednisone at the time of diagnosis was a confounding variable. As a result, a high-dose dexamethasone suppression test was performed first, and the entire evaluation was executed in reverse. The initial findings of marked endogenous hypercortisolism definitively made the diagnosis of Cushing syndrome. An undetectable ACTH level was very suggestive that the known right adrenal mass was indeed producing cortisol. However, prior chronic glucocorticoid therapy raised the unlikely possibility that ACTH production from an ectopic source had been suppressed. To clarify this further, the patient was taken off glucocorticoids and placed on ketoconazole to normalize cortisol production. It was only after ACTH levels remained undetectable with adrenostatic therapy that we were convinced that her right adrenal tumor was the etiology of her Cushing syndrome.

As in our case, antiadrenal therapy with ketoconazole can be used to palliate hypercortisolism due to adrenal adenomas or carcinomas, or to adequately prepare patients for adrenal surgery. Ketoconazole is an antifungal agent which inhibits the synthesis of cholesterol in mammals by blocking 14-demethylation of lanosterol.[7,8] It was first recognized to be a potent inhibitor of gonadal and adrenal steroidogenesis after gynecomastia was reported in patients treated for fungal infections. Its use often correlates with a significant decrease in urinary free cortisol and 17-OHCS. Other drugs which act on the adrenal cortex and reliably control cortisol secretion include metyrapone, aminoglutethimide and o,p'DDD (mitotane). The definitive treatment of Cushing syndrome however involves surgical removal of the cortisol, ACTH, or CRH producing tumor. As a word of caution, physicians must plan to treat adrenalectomized patients with adequate glucocorticoids to prevent acute postoperative adrenal insufficiency, since cortisol secretion by the contralateral adrenal gland is usually suppressed.[9]

The prognosis of untreated Cushing syndrome is poor. Plotz et al reported 17 deaths out of 33 patients within 5 years of diagnosis due to infection, cardiovascular or neoplastic disease.[10] A more recent study showed no increase in mortality in treated patients with Cushing syndrome compared with the general population,[11] thus underscoring the need for appropriate diagnosis and treatment.

Incidental adrenal masses are found in approximately 4% of abdominal computed tomography scans performed.[9] The incidence may continue to increase as "screening radiology" becomes more widely available to the general public. A vast majority of these masses are benign, hormonally inactive and can be safely observed over time. However, it is estimated that 20% of these incidental masses are glucocorticoid-secreting adenomas,[12] which may cause classic or subclinical Cushing syndrome.

Subclinical Cushing syndrome refers to autonomous glucocorticoid production in the absence of specific signs and symptoms of Cushing syndrome and is probably much more common than classic Cushing syndrome. Its prevalence is estimated at 78 cases per 100,000 persons in the general population but it is found in 5–20% of patients with incidentally discovered adrenal masses.[12] Patients with subclinical Cushing syndrome have a high prevalence of obesity, hypertension and type 2 diabetes mellitus, and it has been suggested that cortisol-producing adrenal tumors may be a more common, unrecognized cause of the Metabolic Syndrome. Although these patients lack the classic features of Cushing syndrome, a careful history and physical examination often reveals subtle signs of hormone excess such as recent weight gain or skin atrophy. Chronic mild endogenous cortisol excess may have important systemic effects, and these patients seem to have increased cardiovascular risk with greater incidence of hypertension, impaired glucose tolerance, lipid abnormalities and atherosclerotic plaques.[13] It is precisely for this reason that all patients with incidentally discovered adrenal masses should undergo low dose overnight dexamethasone suppression to rule out subtle subclinical hypercortisolism.

CONCLUSION

We presented a patient with Cushingoid features while on high dose glucocorticoids, who was found to have endogenous hypercortisolism secondary to an adrenal adenoma. Our case illustrates the importance of considering endogenous Cushing syndrome in the differential diagnosis of all patients with adrenal masses, even if they are receiving glucocorticoid therapy at the time. Failure to adequately screen such patients can lead to potentially devastating long-term outcomes.

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