Cushing Syndrome Due to Adrenocorticotropin-Independent Macronodular Adrenal Hyperplasia

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Adrenocorticotropin hormone (ACTH)-independent hypercortisolism accounts for a minority of cases of Cushing syndrome. ACTH-independent macronodular adrenal hyperplasia (AIMAH) is an extremely rare cause of ACTH-independent hypercortisolism. This article describes the case of a woman who presented with significant hypertension of recent onset and was found to have AIMAH. The differential diagnosis of Cushing disease and the treatment of AIMAH are reviewed.

CASE PRESENTATION

Patient Presentation and History

A 53-year-old African American woman was referred to our institution for uncontrolled hypertension. She had a history of hypertension for 13 years and was monitoring her blood pressure at home. When she noticed that it was 200/130 mm Hg on several occasions, she called her primary care physician, who referred her to the hospital for further management. Her past medical history was significant for type 2 diabetes, hypertension, and osteoporosis. She was a nonsmoker. Her medications at home included maximum doses of an angiotensin-converting enzyme (ACE) inhibitor, a β-blocker, a calcium-channel blocker, a potassium-sparing diuretic, and a sulfonylurea drug.

Family History

Her mother had hypertension. Her sister was diagnosed with Cushing syndrome at age 41 years, when she presented with an intracranial bleed secondary to uncontrolled blood pressure. Clinical examination and laboratory data for the sister were consistent with ACTH-independent Cushing syndrome, and imaging studies revealed macronodular adrenal hyperplasia. There were no surgical or pathologic diagnoses as the patient's sister refused surgery and died 6 months after the above presentation.

Physical Examination

Physical examination revealed an alert and oriented woman with blood pressure of 200/125 mm Hg, pulse of 88 bpm, and respiratory rate of 14 breaths/min. She was afebrile. She had moon facies, supraclavicular fat pads, central obesity, and abdominal striae. Results of cardiovascular, chest, and neurologic examinations were unremarkable.

Diagnostic Investigations

Routine chemistries were significant for a serum potassium level of 3.2 mmol/L (normal, 3.5–5.0 mmol/L). A 24-hour urine collection revealed a free cortisol level of 850 μg/24 h (normal, 5–50 μg/24 h), metanephrine level of 0.05 mg/24 h (normal, 0.00–0.40 mg/24 h), normetanephrine level of 0.18 mg/24 h (normal, 0.00–0.90 mg/24 h), and vanillylmandelic acid level of 2.6 mg/24 h (normal, 1.4–6.5 mg/24 h). Additional blood chemistries revealed a plasma renin activity of 1.07 ng/mL/h (normal, 0.65–3.20 ng/mL/h), serum aldosterone level of 11 ng/dL (normal, 3–35 ng/dL), dehydroepiandrosterone (DHEA) sulfate level of 65 μg/dL (normal, 0–245 μg/dL), and plasma ACTH less than 2 pg/mL (normal, 9–52 pg/mL).

Computed tomographic (CT) scans of the abdomen revealed marked asymmetric heterogeneously enlarged adrenal glands consistent with macronodular adrenal

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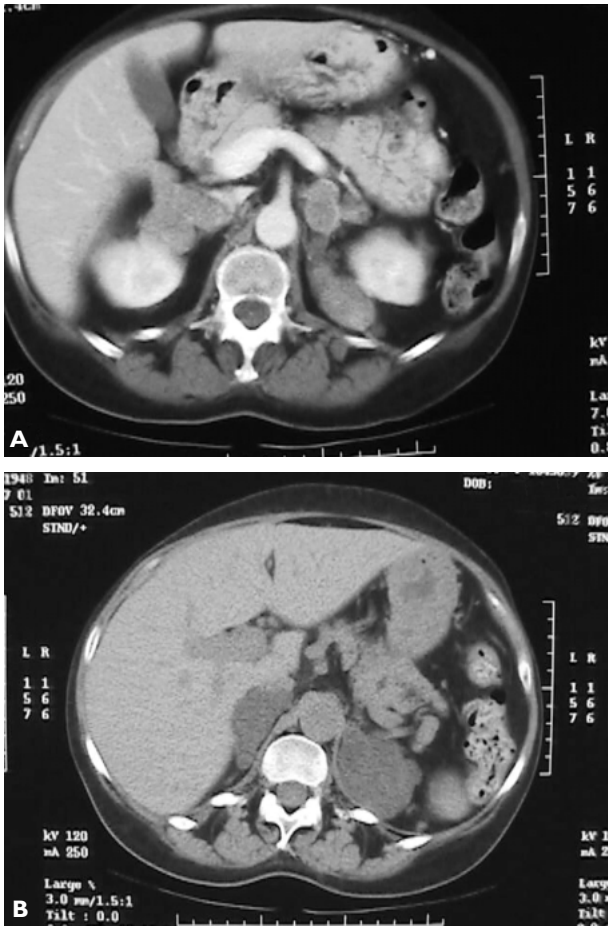

Figure 1. Computed tomographic scans of the case patient that show adrenal enlargement. (**A**) Without contrast media. (**B**) With contrast media.

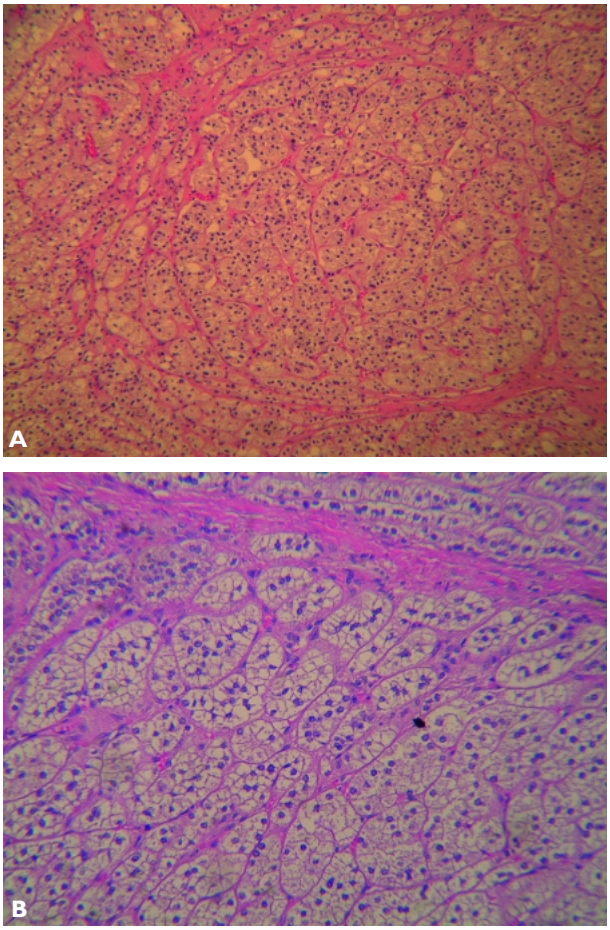

Figure 2. Microscopic views of an adrenal nodule from the case patient. (**A**) Low-power magnification of nodule. (**B**) High-power view showing hyperplastic cells.

hyperplasia (**Figure 1**). Adrenal scintigraphy revealed increased radiotracer uptake in both adrenal glands in early and delayed images consistent with hyperfunctioning adrenal adenomas.

Treatment and Outcome

The patient was started on ketoconazole to block the cortisol. Subsequently, she underwent bilateral adrenalectomy via a posterior approach. The left adrenal gland weighed 55 g and measured 9.5 cm × 5.0 cm × 2.0 cm. The right adrenal gland weighed 86.4 g and measured 11.0 cm × 5.0 cm × 3.5 cm. Sectioning revealed multilobulated, orange-yellow cut surfaces without hemorrhage or necrosis. Microscopy revealed macronodular adrenal hyperplasia (**Figure 2**).

The postoperative course was uneventful and she was placed on physiologic doses of steroid replacement. Six months after surgery, her blood pressure was better controlled, she was off her diabetic medications, and the supraclavicular fat pads were disappearing.

DISCUSSION

Cushing Syndrome

Clinical manifestations. The term Cushing syndrome refers to manifestations of excessive corticosteroids (**Table 1**). The syndrome is commonly due to supraphysiologic doses of glucocorticoid drugs and rarely occurs as a result of spontaneous production of excessive corticosteroids by the adrenal cortex.

In patients with non-iatrogenic Cushing syndrome it is important to distinguish ACTH-dependent forms of hypercortisolism from ACTH-independent forms (**Table 2**). ACTH dependency occurs in approximately 80% of patients with Cushing syndrome. Of these patients, approximately 85% have ACTH-secreting

Table 1. Clinical Manifestations of Cushing Syndrome

General manifestations
Obesity
Hypertension
Skin
Plethora
Hirsutism
Striae
Acne
Bruising
Musculoskeletal
Osteopenia
Weakness
Neuropsychiatric
Emotional lability
Euphoria
Depression
Psychosis
Gonadal dysfunction
Menstrual disorders
Impotence, decreased libido
Metabolic
Glucose intolerance
Diabetes
Hyperlipidemia
Polyuria
Kidney stones

Adapted with permission from Aron DC, Findling JW, Tyrrell BJ. Glucocorticoids and adrenal androgens. In: Greenspan FS, Gardner DG, editors. Basic & clinical endocrinology. 6th ed. New York: Lange Medical Books/ McGraw-Hill; 2001:364.

Table 2. Classification of Cushing Disease

ACTH-dependent
Pituitary adenoma (Cushing disease)
Nonpituitary neoplasm (ectopic ACTH)
ACTH-independent
Iatrogenic causes (glucocorticoid therapy, megestrol acetate)
Adrenal neoplasm (adenoma, carcinoma)
Nodular adrenal hyperplasia (primary pigmented nodular adrenocortical disease, adrenal macronodular hyperplasia)

ACTH = adrenocorticotropin hormone.

pituitary adenomas (ie, Cushing disease) and 15% have ectopic ACTH-secreting tumors.[1]

ACTH-independent hypercortisolism is always of adrenocortical origin, the most common cause being adrenocortical adenoma or carcinoma. Most remaining patients have primary pigmented nodular adrenocortical disease (PPNAD), which can occur sporadically or as a familial disorder with an autosomal dominant inheritance pattern, termed the Carney complex. The Carney complex presents in adolescence or young adulthood and is associated with unusual conditions, such as myxomas (cardiac, cutaneous, and mammary), spotty skin pigmentation, endocrine overactivity (sexual precocity and acromegaly), and schwannomas. The adrenal glands in this disorder are often small or normal in size and have multiple black and brown nodules with intranodular cortical atrophy.[2]

AIMAH is an even rarer form of ACTH-independent hypercortisolism, in which the adrenal glands are massively enlarged and have large nodules. This disorder, also termed adrenal macronodular hyperplasia, is rarely familial.[3–7]

Differential diagnosis. The first step in the diagnosis of a patient with cushingoid manifestations is the overnight dexamethasone suppression test, which is the most valuable screening test in patients with suspected hypercortisolism. In this test, 1 mg of dexamethasone is administered at bedtime, with determination of plasma cortisol levels early the following morning. Failure to suppress the morning cortisol level to lower than 1.8 μg/dL warrants confirmation by assessing the 24-hour urine free cortisol level, which normally is less than 50 μg/24 h. False-negative results of the dexamethasone suppression test may occur in some patients with mild hypercortisolism and in those with intermittent hypercortisolism. False-positive results may occur in chronically ill patients and in those with obesity, depression, alcoholism, or renal failure. False-positive results also occur in patients taking drugs that accelerate dexamethasone metabolism (eg, phenytoin, phenobarbital, rifampin).

Twenty-four hour urine free cortisol determinations usually provide clear discrimination between patients with hypercortisolism and obese non-Cushing patients. As the case patient was obese, the urine free cortisol test was preferred over the dexamethasone suppression test. In addition, renin, aldosterone, and catecholamine levels were assessed to exclude other endocrine causes of hypertension.

Table 3. Clinical Clues to Causes of Secondary Hypertension

Cause	Suggestive Clinical Features
Renovascular disease	Severe or refractory hypertension; an acute elevation in serum creatinine after ACE inhibitor or ARB therapy; moderate to severe hypertension with diffuse atherosclerosis or a unilateral small kidney; repeated episodes of flash pulmonary edema; systolic-diastolic bruit
Primary renal disease	Elevated serum creatinine concentration; abnormal urinalysis results
Oral contraceptives	New elevation in blood pressure temporally related to use
Pheochromocytoma	Paroxysmal elevations in blood pressure with associated headache, palpitations, and sweating
Primary aldosteronism	Unexplained hypokalemia with urinary potassium wasting
Cushing syndrome	Cushingoid facies, central obesity, proximal muscle weakness, and ecchymoses; history of glucocorticoid use
Sleep apnea syndrome	Loud snoring in persons with obesity; daytime somnolence, fatigue, and morning confusion
Coarctation of aorta	Hypertension in the arms with diminished or delayed femoral pulses
Hypothyroidism	Symptoms of hypothyroidism; Elevated serum thyroid-stimulating hormone
Primary hyperparathyroidism	Elevated serum calcium

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

Hypertension is a common finding in patients with endogenous hypercortisolism and may be caused by high levels of other ACTH-dependent steroids such as deoxycorticosterone and corticosterone, which contribute to the mineralocorticoid excess state manifested by hypokalemia and hyporeninemia. Mineralocorticoid-independent mechanisms of hypertension in Cushing syndrome include increased production of angiotensin II; enhanced glucocorticoid-mediated vascular reactivity to vasoconstrictors; inhibition of vasodilatory substances such as kinins and prostaglandins; a shift in sodium from the intracellular to the extracellular compartment, causing increased plasma volume; and an increase in cardiac output caused by the increased production of epinephrine due to enhanced phenylethanolamine-N-methyltransferase activity in the adrenal medulla.

The case patient had low serum potassium levels, but renin, aldosterone, and catecholamine levels were normal. DHEA-sulfate was assessed to make sure that the adrenal mass was not a carcinoma.

The evaluation of a patient with hypertension varies with the likely cause of the elevation in blood pressure. Patients with essential hypertension undergo a relatively limited work-up because extensive laboratory testing is of limited utility. However, clinicians should be aware of the clinical clues that suggest secondary hypertension (**Table 3**).

The next step in the differential diagnosis of Cushing syndrome is to distinguish between ACTH-independent and ACTH-dependent causes by obtaining a plasma ACTH level. In ACTH-independent Cushing syndrome, the level is less than 5 pg/mL and the response to corticotropin-releasing hormone is blunted (ie, peak response < 10 pg/mL).

Adrenal localizing procedures, such as CT scanning and magnetic resonance imaging, are used to define adrenal lesions.[8] Adrenal scintigraphy using ^{131}I-6-β-iodomethyl-19-norcholesterol is a function-dependent imaging method that, in association with high-resolution spatial imaging techniques, plays an essential role in the study of adrenocortical hyperfunction.[9]

The case patient had an elevated urine free cortisol level, low ACTH level, adrenal nodular hyperplasia recognized on CT scan, and bilateral uptake on adrenal scintigraphy consistent with macronodular adrenal hyperplasia. The patient's disease differed from PPNAD by the absence of small pigmented nodules and the absence of features consistent with the Carney complex.[2,10]

ACTH-Independent Macronodular Adrenal Hyperplasia

Epidemiology. The average age of patients with AIMAH is 48 years. The ratio between males and females is equal, and most of the reported cases are from Japan.[11] Kirschner et al reported the first case in 1964,[12] and approximately 110 cases have been reported to date. Familial Cushing syndrome due to AIMAH has been reported in a mother and daughter[5] and in siblings.[8,13]

Pathogenesis. The pathogenesis of AIMAH is unclear. Some authors have proposed a transition from

pituitary (ACTH-dependent) to adrenal-based (ACTH-independent) hypercortisolism,[14] but the rarity of Nelson's syndrome (ie, the clinical appearance of an ACTH-secreting pituitary adenoma following bilateral adrenalectomy) in patients adrenalectomized for macronodular adrenal hyperplasia during 6 to 30 years of follow-up after surgery argues against a transition from ACTH dependence to ACTH independence.[4] Factors other than ACTH that have been suggested as having stimulated the adrenal cortex in reported cases of patients with AIMAH include increased responsiveness to or ectopic production of gastric inhibitory polypeptide receptors,[15] vasopressin receptors,[16] and β-adrenergic receptors.[17]

Treatment and outcome. Ketoconazole, metyrapone, and aminoglutethimide can inhibit adrenal steroid biosynthesis by inhibiting cytochrome P450 enzymes. In daily doses of 600 to 1200 mg, ketoconazole has been effective in the management of Cushing syndrome. These drugs are expensive, however, and their use is accompanied by increased ACTH levels that may overcome the enzyme inhibition. In addition, their gastrointestinal adverse effects limit their effectiveness. Consequently, their use usually is reserved for the preparation of patients for surgery. Mitotane induces remission of hypercortisolism by causing adrenal atrophy in patients with Cushing disease, but most patients relapse after therapy is discontinued. In addition, mitotane has a delayed response and side effects occur frequently.

Bilateral adrenalectomy is the treatment of choice for patients with AIMAH, with subsequent lifelong steroid replacement therapy. A long-term follow-up study of 4 patients with AIMAH showed that unilateral adrenalectomy of the largest gland can be a safe alternative treatment that avoids lifelong steroid replacement and reduces the likelihood of adrenal insufficiency crisis.[18]

Approximately 30% of patients adrenalectomized for Cushing disease develop classic Nelson's syndrome with progressive hyperpigmentation and an ACTH-secreting tumor, another 50% develop evidence of microadenoma without marked progression, and 20% never develop a tumor.[19] Continued examination, including plasma ACTH levels, visual field testing, and sellar radiology is required following bilateral adrenalectomy.

CONCLUSION

The case presented represents a very rare form of ACTH-independent hypercortisolism. The diagnosis was confirmed by pathology. Though the case patient's sister was not diagnosed surgically or pathologically, the clinical, laboratory, and imaging studies pointed toward a diagnosis of AIMAH, making another familial occurrence of this rare disorder. **HP**

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