An Uncommon Presentation of a Common Disease: The Hypertension of Cushing's Syndrome

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Cushing's syndrome is the term used to describe the symptoms and signs of cortisol excess regardless of etiology. Cushing's syndrome can arise from several adrenal and pituitary disorders, whereas Cushing's disease refers to Cushing's syndrome arising from a pituitary disorder. Cushing's syndrome causes only one in 300 hypertension cases and rarely occurs in primary care settings.[1] Hypertension is seen in 58 percent of one compiled series of Cushing's syndrome patients, but hypertension is rarely the reason that patients with Cushing's syndrome consult physicians.[2] The following case report, however, demonstrates the value of a high index of suspicion for recognizing uncommon or rare causes of common problems.

CASE REPORT

A 37-year-old woman was admitted to the medical intensive care unit for management of severe hypertension. At admission her vital signs were normal except for a blood pressure of 240/138 mmHg. She had mild facial flushing, enlarged supraclavicular fat pads, truncal obesity, and striae. Fundi showed slight arteriolar narrowing with indistinct disc margins. Motor strength in the proximal lower extremities was grade 4/5. Speech was pressured and tangential. Electrolytes, blood urea nitrogen, serum creatinine, white blood cell count, and prothrombin and partial thromboplastin times were normal. Random serum glucose was elevated to 11.4 nmol/L (205 mg/dL). Hematocrit was 0.48. Chest roentgenogram and electrocardiogram showed mild left ventricular hypertrophy.

Her past history included hypertension managed intermittently for three years by salt restriction, exercise, hydrochlorothiazide, and propranolol or clonidine. Two and one-half years before admission, her blood pressure reached 166/128 mmHg, and she began to note fatigue, insomnia, palpitations, downy facial hair, oligomenorrhea, loss of libido, and inability to concentrate. A 24-hour urine collection for 17-ketosteroids (17-KS) was normal, and further endocrine workup was recommended, but the patient was lost to follow-up for the next two and one-half years. During this time the patient noted easy bruisability, truncal weight gain, dark abdominal striae, proximal lower extremity weakness, generalized myalgias, shortness of breath, and euphoric mood.

At admission her hypertension was treated with nitroprusside, alpha-methyldopa, hydrochlorothiazide, hydralazine, and later, propranolol. A renal duplex scan was normal. Upon transfer to the family medicine service, it was noted that her unusual habitus and history were consistent with Cushing's syndrome. A morning serum free cortisol determination on blood drawn eight hours after a 1-mg dose of oral dexamethasone was elevated to 990 nmol/L (35.9 μg/dL). A 24-hour urinary free cortisol was 1,900 nmol/d (693 μg/24 h), normal up to 260 nmol/d (93 μg/24 h). Abdominal computerized tomography (CT) showed a 2.5-cm adrenal mass on the right side. Serum adrenocorticotropin (ACTH) levels drawn one hour apart were both normal, less than 6 pmol/L (28 pg/mL). Endocrinology and surgical consultants thought her clinical findings were compatible with adrenal adenoma.

Her preoperative and postoperative care were coordinated by her family physician. She was readmitted to the surgical service for an exploratory laparotomy and removal of a 2.5-cm right-sided adrenal adenoma. She received perioperative prophylactic antibiotics and steroids. A sliding-scale insulin regimen was used for several days postoperatively. Her hypertension required four-drug therapy, which was gradually withdrawn over the three months following adrenalectomy. Depression and anxiety during the first postoperative month were managed by the family physician with supportive counseling and short-acting benzodiazepines. Her prednisone was tapered gradually over the year following adrenalectomy.

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COMMENT

Causes of Cushing's syndrome include pituitary disease (65 to 70 percent of cases), adrenal adenomas and adrenal carcinoma (20 percent), ectopic production of ACTH by tumors (5 to 10 percent), and, rarely, bilateral adrenal hyperplasia unrelated to ACTH secretion.[1,3] Up to 40 percent of patients with Cushing's syndrome have no demonstrable tumor, and a hypothalamic cause is postulated for most of these patients.[4]

One review of 70 patients[5] identified several symptoms and signs useful in the differential diagnosis of Cushing's syndrome. Muscle weakness, bruising, and hypertension were the symptoms most accurate in discriminating Cushing's syndrome from other causes of obesity and hirsutism. Glucose intolerance, headaches, and menstrual irregularities were much less reliable as "discriminatory signs" for Cushing's syndrome. Striae are reported in 40 percent and psychological changes occur in the majority of Cushing's syndrome patients. Proximal weakness is also typical of patients with Cushing's syndrome.

Laboratory findings in Cushing's syndrome can include an elevated hematocrit, serum sodium, creatinine, glucose, triglycerides, and blood urea nitrogen, and a decreased lymphocyte count.[1] A commonly used and reliable screening test for Cushing's syndrome is the overnight low-dose dexamethasone suppression test (1 mg of dexamethasone at 11 PM followed by an 8 AM plasma cortisol determination). This screening test is 98 percent specific for Cushing's syndrome[6,7]; false-positive results are seen mainly in alcoholism, chronic illness, estrogen therapy, obesity, stress, and depression.

Cushing's syndrome can be confirmed by giving 0.5 mg of oral dexamethasone every six hours for two days, with a 24-hour urine 17-hydroxycorticosteroids (17-OHCS) collected on the second day. This test will yield a low value in 98 percent of Cushing's disease patients. Only 6 percent of patients with ectopic ACTH production and no patient with adrenal Cushing's syndrome will have a low 17-OHCS on this test. It is suggested that a baseline 24-hour urine collection for urinary free cortisol, 17-OHCS, and creatinine be performed prior to administration of dexamethasone. Cushing's syndrome causes elevated levels of these steroid compounds: 17-OHCS greater than 11 μmol/d (4 mg/24 h), urinary free cortisol greater than 55 nmol/d (20 μg/24 h), and midnight plasma free cortisol greater than 140 nmol/L (5 μg/dL).[6,7] Adrenal adenomas arise spontaneously, usually producing only glucocorticoids, often intermittently.[1] Random mineralocorticoid levels may be normal in Cushing's syndrome.[8] Adrenal carcinomas are more likely than adrenal adenomas to produce a variety of androgenic steroids such as 17-ketosteroids, dehydroepiandrosterone (DHEA), and DHEA-sulphate (DHEA-S). Hypokalemic alkalosis is

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sometimes seen in patients with ectopic ACTH production.[5] Adrenal causes can be differentiated from pituitary causes with a high-dose dexamethasone suppression test (2 mg of dexamethasone every six hours for two days) and a 24-hour urine collection of 17-OHCS, 17-KS, 17-ketogenic steroids, and free cortisol on the second day after obtaining a baseline level of these compounds. Cortisol production in patients with adrenal Cushing's syndrome or ectopic ACTH production is more difficult to suppress with high doses of dexamethasone than is cortisol production in patients with Cushing's disease.[6]

The accuracy of serum ACTH assays has improved in recent years. Elevated serum ACTH suggests a pituitary tumor or ectopic ACTH production. About two thirds of patients with ectopic ACTH production will have ACTH levels of 44 pmol/L (200 pg/mL or above).[5] If low or normal, in the range of 4 to 22 pmol/L (20 to 100 pg/mL), the cause is most likely adrenal. Because of diurnal variation in ACTH, multiple samples of ACTH are suggested, freezing the sample after collection.

Pituitary, adrenal, and ectopic ACTH-producing tumors can be identified on CT scan. Ultrasound is of little use in detecting small adrenal tumors.[9] Clinically insignificant adrenal nodules up to 3 cm in size may be seen in up to 15 percent of adrenal glands examined at autopsy, especially in patients with hypertension, diabetes, and cardiovascular disease.

Treatment of adrenal tumors causing Cushing's syndrome is surgical. Because of the risk of malignancy, even nonfunctioning tumors should be surgically removed if they occur in patients under 50 years of age, are larger than 3 cm, or increase in size on a subsequent CT scan.[10] Perioperative steroid replacement is usually provided because of the effect of physiological steroid dependency created by the long-standing tumor. Steroid dependency may continue for a few months or up to two years.[5] The physical sequelae of Cushing's syndrome usually improve significantly. In Cushing's syndrome resulting from adrenal adenoma, life expectancy is the same for postadrenalectomy patients as for normal individuals. Untreated, however, patients are at risk for all the complications of hypercortisolism and hypertension. The hypertension of adrenal Cushing's syndrome is more likely to be reversible than the hypertension of Cushing's disease and is less likely if there are pathologic changes in renal or vascular tissue.[11] The prognosis for adrenal carcinoma and ectopic ACTH with its associated malignancies is much worse than for adrenal adenoma.

This case demonstrates that a common condition such as hypertension can arise from an uncommon cause in a primary care setting. Proper diagnosis requires an organized clinical approach with appropriate use of consultants and reassessment when patients do not respond to therapy as expected.

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