Chapter 3
Cushing's Disease

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Objectives

To identify the patient population that should be screened for hypercortisolism, and to understand the approach to the diagnosis, differential diagnosis, and management of Cushing's syndrome.

Case Presentation

A 58-year-old white woman presented with multiple nontraumatic metatarsal stress fractures in both feet. She denied recent falls, corticosteroid use, or prolonged immobility. She did report a progressive weight gain of about 20 pounds over the prior 4 years as well as fatigue, sleep disturbance, hypertension, and hyperlipidemia. Physical exam revealed blood pressure of 150/90 mm Hg and a body mass index (BMI) of 27.5. She was not cushingoid (Fig. 3.1). Her skin did not show significant thinning, acanthosis, or striae. There was some facial rounding but no significant supraclavicular fullness. The physical exam was otherwise unremarkable. Her bone mineral density studies done 18 months prior to the visit showed a low bone density in the hip (T score -1.5) and right femoral neck (T score -2.0), and lumbar spine was normal. Family history was negative for any pituitary, adrenal, thyroid diseases, or osteoporosis.

Because of the weight gain, hypertension, and low bone density with fractures, endogenous hypercortisolism (Cushing's syndrome) was considered. Late-night salivary cortisol levels were elevated at 5.4, 7.3, 7.3, and 8.7 nmol/L (normal range is 0.3–4.3). A 24-hour urine cortisol was 40 μg (normal is less than 45 μg/24 hours). An overnight 1-mg dexamethasone suppression test yielded a cortisol of 20.7 μg/dL (normal is <1.8). Despite the normal 24-hour urine free cortisol, the consistently abnormal late night salivary cortisol measurements as well as the abnormal low

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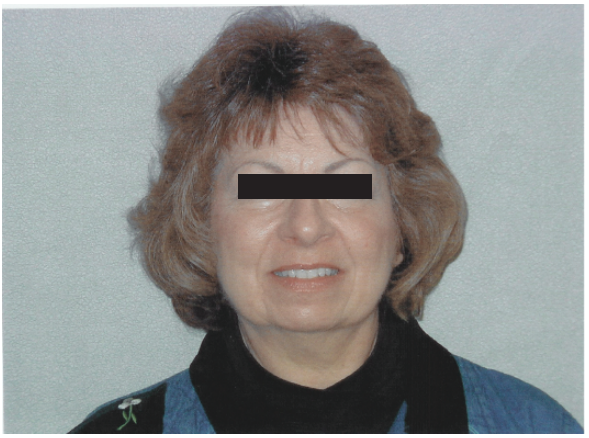

Fig. 3.1 Non-Cushingold woman with weight gain, low bone density, and hypertension

dose dexamethasone suppression test strongly supported the diagnosis of Cushing's syndrome.

To establish the cause of her Cushing's syndrome, a plasma adrenocorticotropin (ACTH) was obtained on two occasions, and the values were elevated at 134 and 117 pg/L (normal range is 9–52). Magnetic resonance imaging (MRI) of the pituitary gland demonstrated a subtle area of asymmetric decreased enhancement within the left portion of the pituitary gland, which could represent a pituitary microadenoma. Since the MRI was not definitive, bilateral simultaneous inferior petrosal sinus ACTH sampling with corticotropin-releasing hormone (CRH) stimulation was performed and demonstrated a significant pituitary to peripheral ACTH gradient as well as an exaggerated ACTH response to CRH (Table 3.1). Based on the results of the inferior petrosal sinus sampling, the diagnosis of Cushing's disease was confirmed. Transsphenoidal pituitary surgery was performed and a 5-mm ACTH-secreting pituitary microadenoma was successfully removed. Postoperatively, the patient's cortisol level decreased immediately to $<3\ \mu g/dL$ and glucocorticoid support was initiated. Seven days after surgery, the patient developed severe hyponatremia requiring rehospitalization. She recovered promptly with fluid restriction.

Table 3.1 Sample location and ACTH concentration (pg/mL)

Time	Right petrosal sinus	Left petrosal sinus	Peripheral
−2 minutes	370	654	119
0 minutes	441	579	118
	100 μg oCRH IV		
2 minutes	5240	3960	121
5 minutes	3140	3200	242
10 minutes	3000	3240	296
30 minutes	–	–	335

oCRH, ovine corticotropin-releasing hormone.

How the Diagnosis Was Made

The clinical and biochemical diagnosis of spontaneous Cushing's syndrome is challenging, particularly when the degree of hypercortisolism is mild, as in our patient. A surprisingly high prevalence of endogenous hypercortisolism has been found in certain high-risk groups. For example, studies have found unsuspected Cushing's syndrome in 2% to 5% of patients with poorly controlled diabetes. It is also well appreciated that 6% to 10% of patients with incidentally discovered adrenal nodules ($\geq$2 cm) have biochemical evidence of excessive cortisol secretion. A recent study found unsuspected Cushing's syndrome in as many as 10.8% of patients with osteoporosis and vertebral compressions fractures and in 4.8% of all patients with osteoporosis who were evaluated for a secondary cause. A recent study by Chiodini et al. found.

The clinical manifestations of Cushing's syndrome are protean, and their onset may be quite insidious over a period of many years. The classic clinical features of hypercortisolism should provoke an evaluation. These features include unexplained weight gain with a central distribution and facial rounding, increased supraclavicular and dorsocervical fat accumulation, cutaneous wasting with easy bruising, wide violaceous striae, proximal myopathy, and decreased growth velocity in children. In addition, several disorders known to be caused or aggravated by hypercortisolism should also stimulate consideration of Cushing's syndrome. For example, patients with the dysmetabolic syndrome (diabetes, hypertension, dyslipidemia, polycystic ovary syndrome), hypogonadotropic hypogonadism, and osteoporosis need to be considered for screening. Despite the fact that our patient was not cushingoid, the presence of her low bone density with fractures, weight gain, and hypertension mandated an evaluation for Cushing's syndrome.

The main screening and diagnostic tests for Cushing's syndrome include a late-night salivary cortisol measurement, an overnight 1-mg dexamethasone suppression test, and a 24-hour urine free cortisol. All three of these tests are complementary, but each has limitations. Traditionally, the 24-hour urine free cortisol was considered the gold standard; as our case illustrates, many patients with Cushing's do not have elevations of urine free cortisol and the sensitivity of this test is only 45% to 71% at a specificity of 100%. Multiple urine collections are often needed when the degree of hypercortisolism is mild, and the cumbersome nature of this test makes it less than ideal for repeat testing. Impaired renal function may also falsely decrease the urine free cortisol. Moreover, certain conditions such as alcoholism, depression, and eating disorders (pseudo-Cushing's syndrome) may result in elevations of urine free cortisol without a pathologic cause of Cushing's syndrome.

The first biochemical detectable abnormality in patients with Cushing's syndrome is the failure to decrease cortisol secretion to its normal nadir at night. This phenomenon has been utilized in the diagnosis of Cushing's syndrome by employing nocturnal salivary cortisol determinations. Salivary cortisol is a reflection of free cortisol and is unaffected by salivary flow rates. Nocturnal salivary cortisol (between 11 p.m. and midnight) yields a sensitivity and specificity approaching 95% for Cushing's syndrome and is emerging as the most reliable and simple diagnostic

test for this disorder. Although, normal ranges differ depending on assay methodology, the use of a Food and Drug Administration (FDA)-cleared enzyme-linked immunosorbent assay (ELISA) for the diagnosis of Cushing's syndrome has provided clinicians with a valuable and reliable diagnostic test. Using this ELISA assay, late-night salivary cortisol levels in normal subjects are consistently less than 3 to 4 nmol/L. Values consistently above 7 nmol/L are virtually diagnostic of Cushing's syndrome, and intermediate values require additional diagnostic evaluation. The screening test used in our patient for the consideration of Cushing's syndrome was nocturnal salivary cortisol, and her levels were between 5.4 and 7.3 nmol/L and certainly raised concern for Cushing's syndrome.

Low-dose dexamethasone suppression testing continues to be widely employed in the diagnostic evaluation of patients with suspected endogenous hypercortisolism. Normal ACTH-secreting cells decrease ACTH release following low doses of dexamethasone as a result of glucocorticoid negative feedback. In contrast, ACTH-secreting neoplasms do not fully suppress ACTH in response to low-dose dexamethasone, resulting in persistent elevations of cortisol. Two forms of the test have been used: a 2-day low-dose dexamethasone suppression test with collection of urine steroids, or an overnight 1-mg dexamethasone suppression test. The former study has been essentially abandoned due to its cumbersomeness. The overnight 1-mg dexamethasone suppression test has the same level of sensitivity and is much easier to perform. Cutoff values for suppression of cortisol following an overnight 1-mg dexamethasone measurement test have been reported between 1.8 and 5 μg/dL. Depending on which value you choose, the sensitivity and specificity obviously change. To achieve a very high sensitivity, a consensus statement suggested that a serum cortisol should be less than 1.8 μg/dL (50 nmol/L) following the overnight 1-mg test; however, this cutoff value results in a less than optimal specificity with significant number of false-positive results. False-positive results can also be caused by decreased dexamethasone absorption (in patients with chronic renal failure), drugs that accelerate hepatic dexamethasone metabolism (anticonvulsant therapy), an increase in cortisol-binding globulin (estrogen therapy), and the aforementioned pseudo-Cushing's conditions (alcoholism, depression, and eating disorders). Despite these limitations, the overnight 1-mg dexamethasone suppression test was helpful in our patient, providing further evidence for the diagnosis of Cushing's syndrome.

Once the diagnosis of Cushing's syndrome is established, the next step is determining its cause. The majority of patients with Cushing's syndrome have an ACTH-secreting neoplasm (ACTH-dependent Cushing's syndrome) usually a pituitary tumor (Cushing's disease) or occasionally a nonpituitary neoplasm (ectopic ACTH). The ectopic ACTH syndrome (particularly when due to neuroendocrine tumors such as bronchial carcinoids) may present with hypercortisolism long before a neoplasm is evident radiographically (occult ectopic ACTH syndrome). These subtypes of ACTH-dependent Cushing's syndrome are often clinically and biochemically indistinguishable and careful differential diagnostic evaluation is required.

In contrast, ACTH-independent Cushing's syndrome is due to autonomous adrenal production of cortisol (adrenal-dependent Cushing's syndrome). The

majority of such patients have a solitary, benign (or, rarely, malignant) adrenocortical neoplasm. A minority have an ACTH-independent form of bilateral nodular adrenal hyperplasia.

The initial step in the differential diagnosis is the measurement of plasma ACTH. A two-site immunometric assay has provided sensitive, specific, and reliable information. A suppressed ACTH (less than 5 pg/mL) indicates adrenal-dependent Cushing's syndrome, and imaging of the adrenal glands is needed. Plasma ACTH levels greater than 20 pg/mL suggest an ACTH-dependent cause. Values between 5 and 20 pg/mL are sometimes more difficult to characterize, and occasionally a CRH stimulation test is required for differential diagnosis. Theoretically, patients with ACTH-independent Cushing's syndrome usually have a subnormal peak ACTH response to CRH (usually less than 30 pg/mL), while patients with pituitary ACTH-secreting neoplasm usually have an exaggerated ACTH response to CRH.

Our patient had a markedly elevated plasma ACTH providing unequivocal evidence that she had an ACTH-secreting neoplasm. Since the majority of patients with ACTH-secreting tumors have pituitary microadenomas (Cushing's disease), the next step is a pituitary MRI. This procedure demonstrates a discrete microadenoma in approximately 40% to 60% of patients with Cushing's disease. When an unequivocal pituitary adenoma (greater than 6 mm) is identified with MRI, further diagnostic evaluation may not be needed and referral to a pituitary neurosurgeon can be recommended. However, it should be remembered that 10% of the normal population has incidental tumors of the pituitary gland found on MRI, although the majority are less than 6 mm. Our patient had equivocal MRI findings, and because of the marked elevation of plasma ACTH, the diagnosis of an occult ectopic ACTH secreting neoplasm was considered.

The only reliable means of distinguishing between pituitary and nonpituitary ACTH-dependent Cushing's syndrome in patients with negative imaging studies is the use of bilateral simultaneous inferior petrosal sinus sampling for ACTH. This test takes advantage of the venous drainage of the anterior pituitary through which hormones such as ACTH reach the systemic circulation. Blood leaves the anterior lobe by numerous small hypophyseal veins that empty directly into the lateral adenohypophyseal veins that converge into the confluent pituitary veins that surround the pituitary gland and then course laterally to join the cavernous sinus and eventually into the inferior petrosal sinus. Inferior petrosal sinus sampling with CRH stimulation provides excellent diagnostic sensitivity and specificity for the diagnosis of Cushing's disease; a central–peripheral ACTH gradient >3.0 is consistent with this diagnosis. The inferior petrosal sinus ACTH sampling results in our patient showed unequivocal evidence of a pituitary ACTH gradient, and the patient was referred to a pituitary neurosurgeon.

Our patient was found to have a 5-mm ACTH-secreting pituitary tumor that was successfully removed and then followed promptly by secondary adrenal insufficiency with very low serum cortisol determinations. The development of secondary adrenal insufficiency after surgery is a good prognostic sign. The majority of these patients have gratifying clinical and biochemical remissions of their Cushing's syndrome. Nonetheless, recurrences may occur, and long-term assessment of pituitary

adrenal function is essential in these patients. Exogenous glucocorticoid support was administered in our patient to help attenuate the problems with steroid withdrawal.

Our patient developed severe, symptomatic hyponatremia approximately 1 week after surgery. This phenomenon (the syndrome of inappropriate antidiuretic hormone) is a well-known complication of pituitary surgery. Theoretically, this is caused by ischemia of the neurohypophysis that occurs at surgery followed by necrosis and an abrupt release of vasopressin (antidiuretic hormone) 5 to 10 days postoperatively, often after the patient has been discharged. As in this patient, hospitalization is often required, with fluid restriction. As in our patient, this problem usually resolves spontaneously without any long-term sequelae. Rarely, patients develop permanent diabetes insipidus.

Lessons Learned

The diagnosis of mild Cushing's syndrome requires a high index of clinical suspicion, particularly in patients with clinical disorders that are caused by or aggravated by hypercortisolism. The presence of unexplained weight gain, hypertension, and low bone density with fractures resulted in a screening study in our patient, who did not have the clinical appearance of Cushing's syndrome. It is clear that the nocturnal salivary cortisol level is a reliable and sensitive screening test for this disorder and should be employed early in the diagnostic evaluation of these patients. Despite normal urinary free cortisol levels in our patient, ACTH-dependent Cushing's syndrome was confirmed with persistent elevations of late-night salivary cortisol and a grossly abnormal low-dose dexamethasone suppression test. The differential diagnosis was quite straightforward with marked elevations of plasma ACTH and an unequivocal pituitary ACTH gradient during inferior petrosal sinus sampling. Pituitary microsurgery resulted in resection of her corticotroph microadenoma followed by clinical and biochemical evidence of adrenal insufficiency portending a good long-term prognosis.

Suggested Readings

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Multiple-Choice Questions

1. Appropriate screening tests for Cushing's syndrome include which of the following?

   A. Pituitary MRI
   B. 24-hour urine free cortisol
   C. Plasma ACTH
   D. Inferior petrosal ACTH sampling
   E. Late-night salivary cortisol

2. After the diagnosis of Cushing's syndrome has been established, the initial diagnostic study should be which of the following?

   A. Pituitary MRI
   B. Dexamethasone suppression testing
   C. Plasma ACTH
   D. CT scan of the adrenal glands
   E. Inferior petrosal sinus ACTH sampling

3. A 35-year-old woman with the insidious onset of the signs and symptoms of hypercortisolism has late-night salivary cortisol values of 19 and 21 nmol/L (normal: 0.3–4.3). Plasma ACTH is 44 pg/mL (normal: 9–52). The most likely cause of her hypercortisolism is which of the following?

   A. Adrenocortical adenoma
   B. ACTH-secreting bronchial carcinoid
   C. ACTH-secreting pituitary tumor
   D. Surreptitious use of prednisone
   E. Anorexia nervosa