Cushing’s Syndrome

Series Editors:
Paul R. Conlin, MD  
Assistant Professor of Medicine, Harvard Medical School,  
Director, Endocrinology, Diabetes and Metabolism Training Program,  
Brigham and Women’s Hospital, Boston, MA

Bryan McIver, MB, PhD  
Consultant in Endocrinology, Mayo Clinic and Foundation,  
Rochester, MN

Contributors:
Erik K. Alexander, MD  
Instructor in Medicine, Harvard Medical School, Division of  
Endocrinology, Diabetes and Hypertension, Brigham and Women’s Hospital, Boston, MA

Robert G. Dluhy, MD  
Professor of Medicine, Harvard Medical School, Division of  
Endocrinology, Diabetes and Hypertension, Brigham and Women’s Hospital, Boston, MA

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INTRODUCTION

In 1932, Harvey W. Cushing described a syndrome resulting from long-term exposure to excessive glucocorticoids. Today, Cushing’s syndrome is known to be a disorder of cortisol excess that has several potential causes, both endogenous and exogenous. In most cases, the endogenous causes are categorized as being either dependent or independent of adrenocorticotropic hormone (ACTH) [Table 1]. Categorizing potential etiologies of Cushing’s syndrome is based on demonstrating autonomous cortisol production and then measuring serum ACTH concentrations.

ACTH-dependent etiologies, such as primary pituitary ACTH hypersecretion (termed Cushing’s disease) by a pituitary adenoma or ectopic ACTH production, are most common and cause continuous hypersecretion of cortisol and adrenal androgens due to unregulated ACTH stimulation. Despite elevated serum cortisol concentrations, serum ACTH values are inappropriately normal or elevated, as the neoplastic cells (from a pituitary adenoma or another, nonendocrine tumor) fail to exhibit the normal negative feedback inhibition of ACTH secretion. ACTH-independent causes result from the hypersecretion of cortisol by neoplasms or from abnormal regulation of the adrenal cortex. In this setting, there is chronic suppression of anterior pituitary ACTH secretion, frequently with atrophy of the cortisol- and androgen-producing zones of the contralateral adrenal cortex.

The prevalence of endogenous Cushing’s syndrome has been estimated to be about 10 cases per million, although in subgroups of obese individuals the prevalence may be greater. This figure would be considerably larger if it included the most common cause of hypercortisolism—oral ingestion of prescribed glucocorticoids for the treatment of various nonendocrine illnesses. Cushing’s syndrome also may be caused by exogenous administration of glucocorticoids via topical, injected, or inhaled routes, although clinical features of Cushing’s syndrome are generally mild. Thus, when there is clinical suspicion of an excessive glucocorticoid state, a detailed history and review of current medications is essential.

The diagnosis of Cushing’s syndrome may be obvious in severe cases, but can be challenging when the degree of excess cortisol is mild. On initial examination, differentiating patients with Cushing’s syndrome from the large number of patients with Cushing’s syndrome phenotype is often difficult. Furthermore, several conditions can cause abnormal elevations of serum, urinary, or salivary cortisol and therefore biochemically mimic Cushing’s syndrome. This disorder has been termed pseudo-Cushing’s syndrome.

When evaluating patients suspected of having Cushing’s syndrome, it is important first to document autonomous cortisol production and then measuring serum ACTH concentrations. ACTH-dependent etiologies, such as primary pituitary ACTH hypersecretion (termed Cushing’s disease) by a pituitary adenoma or ectopic ACTH production, are most common and cause continuous hypersecretion of cortisol and adrenal androgens due to unregulated ACTH stimulation. Despite elevated serum cortisol concentrations, serum ACTH values are inappropriately normal or elevated, as the neoplastic cells (from a pituitary adenoma or another, nonendocrine tumor) fail to exhibit the normal negative feedback inhibition of ACTH secretion. ACTH-independent causes result from the hypersecretion of cortisol by neoplasms or from abnormal regulation of the adrenal cortex. In this setting, there is chronic suppression of anterior pituitary ACTH secretion, frequently with atrophy of the cortisol- and androgen-producing zones of the contralateral adrenal cortex.

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ACTH-DEPENDENT CUSHING’S SYNDROME

CASE 1
Initial Presentation

A 27-year-old man is referred to an endocrinologist for evaluation of weight gain, hypertension, and proximal muscle weakness.

History

The patient was in good health until 18 months ago, when he noted a gradual change in his normal level of energy. Although he had always been athletic, he found it more difficult to exercise because of fatigue and muscle weakness. He noticed that he began to gain weight, which was apparent when he compared his appearance to that in prior photographs. On a visit
to his primary care physician 1 year ago, he was found to have gained 30 lb over 6 months, and his blood pressure was 146/98 mm Hg. He was subsequently given recommendations to change his diet and increase his level of exercise.

At a recent visit to his primary care physician, the patient reported having difficulty adhering to his exercise prescription and to losing weight. He complained that his energy persisted in being low and he was feeling more irritable lately, which he attributed to worsening insomnia. He was disturbed by the extra weight he was carrying, particularly the fat he had developed on the back of his neck. Examination revealed no change in the patient’s weight, a blood pressure of 144/96 mm Hg, and proximal muscle weakness. These findings prompted referral for evaluation of a possible endocrine disorder.

In addition to the history reported thus far, the endocrinologist learns that over the past 6 months the patient has noted purple “stretch marks” on the sides of his abdomen, which have continued to enlarge. He also has found that he bruises easily with minimal trauma. Finally, he says that his friends and family tease him about going to a tanning salon, since he seems to “maintain his tan” so long after the summer months.

The patient had a normal childhood and adolescence, with no other medical problems. He currently takes no medications and does not smoke. There is no family history of endocrine disorders, although a paternal grandfather suffered a kidney stone.

### Physical Examination

The patient has marked central adiposity and thin, atrophic extremities. His blood pressure is 144/94 mm Hg and pulse is 80 bpm. Head examination is notable for a round appearance, and moderate acnec is noted on his back. The patient is diffusely pigmented, and his buccal mucosa is darkened. His skin is thin, and resolving greenish-blue ecchymoses are present on his arms, legs, and shoulders. Abdominal examination is notable for violaceous striae, 1.0 to 1.5 cm in width, on his lateral abdomen. Cardiac and pulmonary examinations are normal.

**How should this patient’s clinical presentation be interpreted?**

### CLINICAL FEATURES OF CUSHING’S SYNDROME

This patient presents with several clinical features consistent with hypercortisolism and suggestive of increased cortisol secretion, as no exogenous source is evident. Excessive production of cortisol leads to a variety of systemic effects (Table 2), which, depending on the severity and duration of the hypercortisolism, often progress and evolve over time. Many of the clinical manifestations of Cushing’s syndrome tend to be less severe in patients older than age 50 years. No single feature, however, is pathognomonic. The most prominent features are due to cortisol overproduction and are therefore independent of the etiology. However, some features such as skin hyperpigmentation (secondary to increased ACTH secretion) and adrenal androgen

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**Table 1. Causes of Endogenous Cushing’s Syndrome and their Relative Frequencies**

<table>
<thead>
<tr>
<th>ACTH-dependent Cushing’s syndrome (~80%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s disease (pituitary adenoma)</td>
<td></td>
</tr>
<tr>
<td>Ectopic ACTH production</td>
<td></td>
</tr>
<tr>
<td>Ectopic CRH production</td>
<td></td>
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<tr>
<td>ACTH-independent Cushing’s syndrome (~20%)</td>
<td></td>
</tr>
<tr>
<td>Adrenocortical adenoma</td>
<td></td>
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<tr>
<td>Adrenocortical carcinoma</td>
<td></td>
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<tr>
<td>Bilateral micronodular hyperplasia (Carney’s syndrome; &lt; 1%)</td>
<td></td>
</tr>
<tr>
<td>Macronodular hyperplasia (GIP or food-dependent Cushing’s syndrome; &lt; 1%)</td>
<td></td>
</tr>
</tbody>
</table>

**ACTH = adrenocorticotropic hormone (corticotropin); CRH = corticotropin-releasing hormone; GIP = gastric inhibitory polypeptide.** (Adapted with permission from Orth DN. Cushing’s syndrome. N Engl J Med 1995;332:791–803. Copyright 1995 Massachusetts Medical Society. All rights reserved.)

**Table 2. Signs and Symptoms of Cushing’s Syndrome**

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Central obesity</td>
<td>79–97</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47–90</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>78–94</td>
</tr>
<tr>
<td>Weakness</td>
<td>56–90</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>39–90</td>
</tr>
<tr>
<td>Menstrual irregularity</td>
<td>55–80</td>
</tr>
<tr>
<td>Psychiatric changes</td>
<td>35–86</td>
</tr>
<tr>
<td>Acne</td>
<td>26–80</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>60–77</td>
</tr>
<tr>
<td>Buffalo hump</td>
<td>34–67</td>
</tr>
<tr>
<td>Striae</td>
<td>50–64</td>
</tr>
</tbody>
</table>

Adapted from Howlett TA, Rees LH, Besser GM. Cushing’s syndrome. Clin Endocrinol Metab 1985;14:916, with permission from Elsevier Science.
overproduction are found primarily in patients with ACTH-dependent Cushing’s syndrome.

The most common clinical findings in patients with Cushing’s syndrome are obesity, hypertension, and facial plethora. Although generalized obesity itself is nonspecific, localized fat accumulations in the cheeks and face (moon facies), dorsocervical region (buffalo hump), and especially in the supraclavicular fossae, are highly specific for hypercortisolism. Patients with Cushing’s syndrome also experience a disproportionate increase in intra-abdominal or visceral fat compared with the generalized accumulation of adipose tissue seen in simple obesity. This finding is very helpful during the initial clinical examination of overweight individuals referred for evaluation of cortisol excess.

Dermatologic manifestations occur in only 50% to 60% of patients but are among the most specific markers of Cushing’s syndrome. Thinning of the skin due to atrophy of the stratum corneum and loss of subcutaneous fat are classic features. As a result, patients often report frequent bruising with ecchymoses following minimal trauma. In extreme cases, the skin may peel off when adhesive tape is applied, similar to wet tissue paper (Liddle’s sign). The skin also is stretched and forms striae that appear purplish or red because of the subcutaneous blood vessels visible beneath an atrophic epidermis. Unlike striae associated with pregnancy, those associated with Cushing’s syndrome often occur on the lateral abdomen and flanks (as opposed to the periumbilical area), are discolored (as opposed to silver), and are greater than 1 cm in width.

Hyperpigmentation occurs in Cushing’s syndrome secondary to excessive ACTH secretion from a pituitary adenoma (Cushing’s disease) or to ectopic ACTH syndrome. It is a manifestation of excessive action of ACTH—and of other pro-opiomelanocortin peptides such as melanocyte-stimulating hormone—on skin melanocytes. The skin darkening may be noted on such as melanocyte-stimulating hormone—on skin (ACTH)—and of other pro-opiomelanocortin peptides syndrome. It is a manifestation of excessive action of ACTH—and of other pro-opiomelanocortin peptides such as melanocyte-stimulating hormone—on skin melanocytes. The skin darkening may be noted on such as melanocyte-stimulating hormone—on skin melanocytes. The skin darkening may be noted on such as melanocyte-stimulating hormone—on skin melanocytes. The skin darkening may be noted on such as melanocyte-stimulating hormone—on skin melanocytes. The skin darkening may be noted on such as melanocyte-stimulating hormone—on skin melanocytes. 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Psychiatric complications may be variable in presentation. Emotional lability, depression, insomnia, and generalized loss of energy are frequent complaints and are direct effects of cortisol excess on the central nervous system.

- **What tests should be ordered for this patient at this time?**

**CONFIRMING HYPERCORTISOLISM**

The first step in evaluating a patient in whom Cushing’s syndrome is suspected is to document autonomous hypercortisolism. Most often, a 24-hour urinary free cortisol (UFC) measurement or an overnight (1 mg) dexamethasone suppression test is performed as the initial screening test. A 24-hour UFC measurement in the normal range (ie, less than 50 µg/24 hr) effectively rules out the diagnosis of Cushing’s syndrome, whereas levels greater than three times the upper limit of normal are supportive of the diagnosis. Values between one and three times the upper limit of the normal range are consistent with either Cushing’s syndrome or pseudo-Cushing’s syndrome; in the appropriate clinical setting, such results warrant further testing, such as serial 24-hour UFC measurements and/or dexamethasone testing. Similarly, a morning plasma cortisol level less than 5 µg/dL following 1 mg of dexamethasone administered the previous night is predictive of normal hypothalamic-pituitary-adrenal physiology; some have suggested that lower levels (ie, less than 2 µg/dL) may be more specific. A value greater than 10 µg/dL is highly suggestive of Cushing’s syndrome, and values between 5 and 10 µg/dL often prompt additional testing. By adhering to these guidelines, false-negative results will be minimized, although a significant number of false-positive results may still occur.

When further evaluation is needed, several different tests can be performed to provide more data. Although inconvenient, measurement of midnight plasma cortisol concentration can often be very helpful in difficult cases, as patients with Cushing’s syndrome lose the evening nadir of plasma cortisol found in normal individuals. A value less than 5 µg/dL (138 nmol/L) virtually rules out Cushing’s syndrome, whereas values greater than 7.5 µg/dL (207 nmol/L) support the diagnosis. Intermediate values are less helpful. An alternative to measuring midnight plasma cortisol concentration is to measure salivary cortisol concentration, which is easier for most patients.

If the diagnosis still remains in doubt, the patient should be evaluated using a combination of low-dose
Cushing’s Syndrome

dexamethasone suppression and corticotropin-releasing hormone (CRH) stimulation testing. A low dose (0.5 mg) of dexamethasone is administered every 6 hours, eight times over 2 days, beginning at 12 noon on day 1. Following the final dose of dexamethasone, a CRH stimulation test (1 µg/kg) is performed at 8 AM. A plasma cortisol concentration greater than 1.4 µg/dL measured 15 minutes after the administration of CRH correctly identifies patients with Cushing’s syndrome.

BIOCHEMICAL EVALUATION OF CASE PATIENT

Suspecting Cushing’s syndrome, the endocrinologist initially orders a 24-hour UFC measurement, which is 289 µg/24 hr (normal, less than 50 µg/24 hr). Two weeks later, the patient’s serum ACTH concentration is measured at 50 pg/mL (normal, 9 to 52 pg/mL).

• What is the appropriate next step in the evaluation of this patient?

DETERMINING THE SOURCE OF ACTH OVERPRODUCTION

This patient’s 24-hour UFC measurement is more than three times the upper limit of the normal range, confirming the diagnosis of Cushing’s syndrome. His serum ACTH concentration is within the normal range but inappropriately elevated in the setting of marked hypercortisolism. Thus, this patient has ACTH-dependent Cushing’s syndrome. The majority of his symptoms are attributable to excess cortisol production, although the hyperpigmentation of his skin and buccal mucosa reflects ACTH overproduction. With the diagnosis of ACTH-dependent Cushing’s syndrome established, further evaluation is now needed to determine the source of the ACTH overproduction.

Potential Causes

The ACTH-dependent varieties of Cushing’s syndrome include Cushing’s disease (pituitary ACTH hypersecretion from a pituitary adenoma), ectopic ACTH hypersecretion (from a nonpituitary tumor), and ectopic CRH hypersecretion (from a nonpituitary tumor). These conditions all cause bilateral adrenal hyperplasia due to the trophic effects of ACTH.

Cushing’s disease. ACTH hypersecretion from a pituitary adenoma is the most common form of Cushing’s syndrome, accounting for about 65% to 75% of all cases of endogenous hypercortisolism. The tumors usually are benign and small (less than 1 cm in diameter). Up to 50% are not visualized with magnetic resonance imaging (MRI). The pituitary adenoma in Cushing’s disease is monoclonal and arises from a single progenitor cell, as opposed to generalized corticotroph hyperplasia (as seen in ectopic CRH hypersecretion).

Dynamic testing of patients with Cushing’s disease reveals a pattern of partial resistance of ACTH secretion to glucocorticoid negative feedback. Thus, the pituitary adenoma functions at a higher than normal feedback set-point. This finding may be exploited to support the diagnosis of Cushing’s disease using the high-dose (8-mg) overnight dexamethasone suppression test.

Ectopic ACTH or CRH hypersecretion. Most cases of ectopic ACTH or CRH hypersecretion are associated with small-cell lung carcinoma. Because of the often fulminant nature of these syndromes, patients may present with biochemical features of severe hypercortisolism including the rapid onset of hypertension, edema, hypokalemia, and glucose intolerance. A more chronic form of these syndromes can also occur, caused by ACTH and/or CRH hypersecretion from bronchial carcinoid tumors. Unlike ACTH secretion from pituitary corticotroph tumors, ACTH secretion from ectopic tumors usually is not suppressible by glucocorticoids. However, this rule is not invariable, as some glucocorticoid-induced ACTH suppression is seen in up to half of carcinoid tumors.

Diagnostic Approach

Tests to determine the source of ACTH overproduction take advantage of the finding that patients with Cushing’s disease retain partial suppression of ACTH and cortisol following glucocorticoid administration. Either a 2-day, high-dose dexamethasone suppression test (2 mg every 6 hours for eight doses) or 8-mg overnight dexamethasone suppression test can be performed. If 24-hour urinary cortisol excretion is suppressed by greater than 90% from baseline during the 2-day test or a morning plasma cortisol is less than 50% of baseline (following the 8-mg overnight test), the diagnosis of Cushing’s disease is likely. Patients with evidence of a pituitary microadenoma typically are referred for surgery.

If pituitary imaging studies are normal, inferior petrosal sinus catheterization and sampling (IPSS) with measurement of ACTH levels before and after exogenous CRH stimulation can help to identify whether the excess ACTH is from the pituitary gland or an ectopic source. In this procedure, a catheter is positioned in each inferior petrosal sinus, and blood samples are taken simultaneously from both sinuses as well as from a peripheral vein. These samples are drawn twice before and twice after CRH administration. An inferior petrosal sinus-to-peripheral blood (IPS:P) ratio greater
Cushing’s Syndrome

than 2.0 identifies 95% of patients with Cushing’s disease, with 100% specificity. A peak ratio greater than 3.0 after CRH stimulation correctly identifies nearly all patients with Cushing’s disease.17 However, recent studies have suggested some caution with this test.18 Although IPSS often is highly effective, success with this procedure and avoidance of complications largely depend on the skill and experience of the interventional radiologist.18

FURTHER EVALUATION OF CASE PATIENT

The patient undergoes a 2-day, high-dose (8-mg) dexamethasone suppression test. The 24-hour UFC measurement on day 2 of the test is 30 µg/24 hr. Pituitary MRI reveals a 6-mm, low-intensity lesion in the right anterior lobe of the pituitary gland.

- What is the appropriate treatment of this patient?

TREATMENT OF ACTH-DEPENDENT CUSHING’S SYNDROME

The treatment of ACTH-dependent Cushing’s syndrome is dictated by the cause of ACTH hypersecretion.

Cushing’s Disease

Pituitary surgery. Treatment for Cushing’s disease is directed at the pituitary gland, with transsphenoidal surgery the therapy of choice. In experienced hands, a cure rate of 80% to 90% for microadenomas can be achieved; for macroadenomas (ie, tumors greater than 1 cm in diameter), the cure rate is reduced to less than 50%.10,19,20 To assess cure, an early morning serum cortisol concentration can be measured in the days immediately following surgery and should be less than 2 µg/dL (56 nmol/L) in “cured” patients. Plasma ACTH should be undetectable as well. Although initial “cure” rates are very high, long-term normalization of cortisol secretion is probably achieved in only 60% to 70% of patients with microadenomas, due to tumor recurrence. For patients with recurrent disease, treatment options include repeat surgery, pituitary radiotherapy, and medical or surgical adrenalectomy.

Pituitary radiotherapy. Radiotherapy is the most frequent choice of therapy for recurrent disease, particularly in patients in whom repeat IPSS and/or surgery is contraindicated or carries high risk. Conventional radiotherapy is a noninvasive procedure that rarely is associated with major side effects. The procedure carries a small risk of causing subsequent hypopituitarism or secondary brain malignancy. A total of 42 to 45 Gy (4200 to 4500 rad) of conventional radiation is delivered to the pituitary gland over a period of 12 to 18 months. This regimen is effective in reducing hypercortisolism in approximately 50% of adults and up to 80% of children. Newer methods such as stereotactic gamma knife, α-particle, and/or proton beam radiotherapy may produce even better results, although long-term follow-up studies have not been completed.

Adrenalectomy. In patients in whom rapid cure of hypercortisolism is needed or prior therapy has been ineffective, an adrenolytic medication or surgical adrenalectomy remains an option. Medications that can be given to block cortisol synthesis include mitotane, ketoconazole, aminoglutethimide, and metyrapone. Experience with mitotane has been most extensive and most physicians select this medication; however, the other adrenolytic agents (alone or in an additive fashion) also are effective. When using mitotane, it is often difficult to predict when a patient will fall in cortisol. Therefore, a replacement dose of dexamethasone (0.5 mg/day) usually is administered concurrently. When medication side effects are severe or a more permanent lowering of cortisol is desired, bilateral surgical adrenalectomy is performed. Follow-up pituitary radiotherapy should be considered, if not previously administered, to prevent Nelson’s syndrome (ie, enlarging pituitary adenoma and increased ACTH levels due to loss of negative feedback inhibition by cortisol).

Ectopic ACTH or CRH Hypersecretion

Ectopic ACTH or CRH from a malignant tumor can be treated by primary chemotherapy targeted at the underlying malignancy.

CASE RESOLUTION

Given the high likelihood of Cushing’s disease, the patient undergoes transsphenoidal resection of the pituitary lesion. Histologic sectioning of the lesion reveals an adenoma that is positive for ACTH on immunoperoxidase staining. Plasma ACTH and serum cortisol levels are undetectable 5 days after surgery.

ACTH-INDEPENDENT CUSHING’S SYNDROME

CASE 2

Initial Presentation

A 49-year-old woman is referred to an endocrinologist for evaluation of hirsutism and weight gain.

History

The patient reports that she was in good health until 2 years ago, when she noted the onset of excessive hair
growth on her face, sternum, and extremities. Although she has been overweight most of her life, she has gained 40 lb over the last 18 months despite attempts at dieting. She additionally complains that she is increasingly fatigued at the end of a normal workday and notes that her colleagues recently mentioned her face appears “flushed” at work. Although she attributes her flushed appearance to menopausal hot flashes, she wonders whether menopause could also explain why she has developed acne on her face. She states that her menses stopped 3 years ago. The patient’s past medical history is notable for hypertension, for which she started therapy with atenolol 5 years ago. She has no family history of endocrine disorders and denies exogenous glucocorticoid use.

Physical Examination
The patient is centrally obese, with thin extremities. Her blood pressure is 134/86 mm Hg and pulse is 80 bpm. She has prominent facial plethora as well as moderate acne and terminal hair growth on her upper lip and chin. Abnormal hair growth is also noted on the dorsum of her arms and sternum and around her umbilicus. Abdominal examination reveals numerous pink striae approximately 1 cm in width located on the lateral flanks. She is unable to arise from a deep knee bend performed during the examination and can arise from a chair only with extensive effort.

Biochemical Evaluation
Suspecting Cushing’s syndrome, the endocrinologist orders a 24-hour UFC measurement, which is 412 µg/24 hr (normal, less than 50 µg/24 hr). In addition, the patient’s serum ACTH concentration is measured at 0.8 pg/mL (normal, 9 to 52 pg/mL).

- What is the most likely explanation for this patient’s clinical presentation and laboratory findings?
- What is the appropriate next step in the evaluation of this patient?

FEATURES OF ACTH-INDEPENDENT CUSHING’S SYNDROME
This patient presents with several signs and symptoms attributable to excess cortisol production (see Table 2), as well as features of adrenal androgen production (acne, hirsutism). Her 24-hour UFC measurement is more than three times the upper limit of the normal range, and her serum ACTH concentration is very low, confirming the diagnosis of ACTH-independent Cushing’s syndrome. ACTH-independent Cushing’s syndrome is less common than Cushing’s disease, occurring in approximately 20% of all individuals with hypercortisolism. Regardless of the etiology, serum cortisol concentrations are elevated and ACTH values are suppressed. Hyperpigmentation, a finding in patients with ACTH-dependent Cushing’s syndrome, is notably absent in ACTH-independent disease.

When Cushing’s syndrome is confirmed and ACTH values are very low or undetectable, an exogenous source of glucocorticoid should first be suspected, as this is the most common cause of ACTH-independent Cushing’s syndrome. However, because this patient denies glucocorticoid use, further evaluation is needed to determine the source of the cortisol overproduction.

DETERMINING THE SOURCE OF CORTISOL OVERPRODUCTION
Possible Causes
After exogenous glucocorticoid use, the most common cause of cortisol overproduction is a neoplasm (usually benign) of the adrenal cortex. Rarely, ACTH-independent Cushing’s syndrome can be caused by bilateral micronodular or macronodular hyperplasia.

Adrenocortical tumors. It is difficult to differentiate adrenal adenomas from carcinomas based on cytologic features alone. Instead, the presence of capsular invasion and/or metastatic spread is required to confirm the diagnosis of carcinoma. Biochemically, adrenal adenomas are highly efficient steroid-producing neoplasms, usually producing only cortisol. In contrast, adrenal carcinomas are characteristically inefficient and produce several steroid intermediates and end products. In patients with adrenal adenomas, urinary excretion of adrenal androgens such as 17-ketosteroids often is low in relation to excretion of 17-hydroxycorticosteroids and free cortisol. The opposite may occur in patients with adrenal carcinoma. Additionally, whereas patients with adrenal adenomas usually experience a gradual onset of hypercortisolism, those with adrenal carcinomas often experience rapid and fulminant disease. The occurrence of flank, back, or buttock pain (likely due to expansion of the adrenal capsule) also suggests the possibility of a malignant tumor.

Bilateral micronodular and macronodular adrenal hyperplasia. About 50% of cases of bilateral micronodular hyperplasia occur spontaneously in children and young adults; the other 50% occur as part of an autosomal dominant familial disorder (eg, Carney complex) associated with blue nevi, atrial myxomas, and other rare tumors. Bilateral macronodular hyperplasia has been reported in a few patients who have paradoxical increases in plasma cortisol concentrations following meals, due to adrenocortical stimulation by gastric inhibitory polypeptide (GIP).
Cushing’s Syndrome

Diagnostic Approach

After excluding exogenous steroid use, computed tomography (CT) of the adrenal glands should be performed. Nearly all cortisol-producing tumors are visible on thin-section CT scans. Newer imaging techniques (eg, T2-weighted MRI scans, 131I-labeled cholesterol scans) can assist in the characterization of a mass lesion but are infrequently needed. When the CT scan does not reveal an obvious adrenal mass, the images should be reevaluated for evidence of nodularity. Testing for other manifestations of Carney’s syndrome, such as atrial myxomas, and careful examination of the skin for pigmented nodules also may be needed. Measurement of serum cortisol and GIP concentrations before and after ingestion of food may help to confirm the etiology of the rare bilateral macronodular hyperplasia.

FURTHER EVALUATION OF CASE PATIENT

The patient undergoes adrenal CT scanning and is found to have a 4.4-cm mass in the right adrenal gland.

• What is the appropriate treatment of this patient?

TREATMENT OF ACTH-INDEPENDENT CUSHING’S SYNDROME

Adrenocortical Tumors

In patients with adrenocortical tumors, the primary therapy is surgical resection of the neoplasm. Small adenomas often can be removed via a laparoscopic approach. Larger (greater than 4 cm) neoplasms may require a flank or transabdominal approach, as a possible carcinoma requires a wide excision of the tumor mass. The cure rate for adrenal adenomas is nearly 100%, with relatively few postoperative complications, particularly when performed laparoscopically. The cure rate for adrenal carcinoma, however, is significantly worse and appears unrelated to the size of the tumor at the time of removal. Median survival time for such patients is less than 3 years. Following surgery, all patients (regardless of pathology) will have profound hypocortisolism due to atrophy of the pituitary corticotrophs and the contralateral adrenal cortex. Glucocorticoid therapy is required perioperatively and should be tapered over the next 6 to 12 months to gradually restore the function of the suppressed pituitary gland and contralateral adrenal cortex. If surgical resection is not possible or if hypercortisolism persists following surgery, an adrenolytic medication such as mitotane is indicated to reduce the cortisol levels (see discussion of Adrenalectomy on page 6).

CASE RESOLUTION

The endocrinologist recommends surgical removal of the adrenal mass, and the patient agrees to undergo surgery. Histologic examination of the mass reveals an adrenal carcinoma with evidence of capsular invasion and a high mitotic rate. Postoperative serum cortisol concentrations are undetectable, consistent with complete tumor resection. However, 6 months after surgery symptoms of cortisol excess return, and metastatic disease is confirmed in the surgical bed and liver. The patient is started on mitotane, with subsequent normalization of the serum cortisol concentration. However, adrenal CT scans reveal no objective evidence of a reduction in tumor size.

PSEUDO-CUSHING’S SYNDROME

CASE 3

Initial Presentation

A 39-year-old woman is referred to an endocrinologist for evaluation of possible Cushing’s syndrome.

History

The patient states that she began noting unexplained weight gain 6 years ago, after the birth of her second child, and in the past 4 years has gained 70 lb. She also complains of increasing insomnia and fatigue and feels that the dark hair above her lip, which she has had since puberty, has worsened in recent years. She reports severe emotional lability over the last 6 years, which has led to a diagnosis of major depression and subsequent treatment with medication and counseling. She was hospitalized twice for depression but denies any attempts at self-harm.

The patient has normal menstrual cycles. She has been exercising twice weekly in an attempt to lose weight, and she recently suffered a stress fracture in her right foot. Six months ago, she was diagnosed with glucose intolerance and was given diet and exercise recommendations aimed at preventing progression of hyperglycemia. She denies any history of hypertension, thrush, or kidney stones. She does not use alcohol. Her current medications include a selective serotonin-reuptake inhibitor and a multivitamin. Her family history is notable for obesity in her mother, sister, and maternal grandmother.

Physical Examination

The patient’s blood pressure is 130/86 mm Hg, pulse is 80 bpm, and body mass index is 42 kg/m². She has
Cushing’s Syndrome

some mild facial rounding and slight plethora but no acne. There is a slight increase in supravclavicular fullness. Abdominal examination reveals numerous periumbilical striae that are greater than 1 cm in diameter but are not discolored or violaceous. Her proximal muscle strength is normal, and she has no evidence of hirsutism.

Biochemical Evaluation

As a first step in determining whether this patient has Cushing’s syndrome, the endocrinologist orders a 24-hour UFC measurement. Due to intermediate results, the test is repeated two times over the next 4 months and an overnight dexamethasone suppression test is performed. Results of biochemical testing are as follow:

- 24-hr UFC: 132 µg/24 hr, 49 µg/24 hr, and 72 µg/24 hr (normal, less than 50 µg/24 hr)
- Serum cortisol following overnight 1-mg dexamethasone suppression test: 3.4 µg/dL (normal, less than 5.0 µg/dL)
- Serum cortisol at 11 PM: 3.2 µg/dL (normal, less than 5 µg/dL)

Do these findings support a diagnosis of Cushing’s syndrome?

What, if any, further tests are needed for this patient?

DIFFERENTIATING TRUE CUSHING’S FROM PSEUDO-CUSHING’S SYNDROME

This patient presents with some clinical features suggestive of true Cushing’s syndrome, including obesity, mild facial rounding, glucose intolerance, and emotional lability. However, her urinary cortisol measurements are only mildly elevated, and her late night serum cortisol concentration and overnight dexamethasone suppression test result are normal. These laboratory findings argue against a diagnosis of true Cushing’s syndrome and, combined with the patient’s history of depression, suggest the possibility of pseudo-Cushing’s syndrome.

Depression is one of several conditions that can cause cortisol levels to be abnormally elevated and, thus, biochemically mimic true Cushing’s syndrome (Table 3). Excess cortisol production is an inherent response by the hypothalamic-pituitary-adrenal axis to the underlying illnesses as opposed to true hypothalamic-pituitary-adrenal axis pathology. As a result, primary treatment of the underlying disorder corrects the biochemical hypercortisolism—the sine qua non of pseudo-Cushing’s syndrome. Recognition of pseudo-Cushing states is crucial, given the substantial cost and risk associated with invasive testing and surgery that may otherwise not be necessary. The differentiation of Cushing’s syndrome from pseudo-Cushing’s syndrome also is essential so that the appropriate follow-up testing and therapy can be carried out.

Potential Causes

Depression. Although most patients with depression do not have the typical physical signs of Cushing’s syndrome, a proportion of patients with depression do suffer from obesity, hypertension, and/or diabetes, thus making the clinical diagnosis of Cushing’s syndrome reasonable. In addition, patients with depression can have hormone abnormalities consistent with Cushing’s syndrome, including abnormal responses to most of the usual tests of the hypothalamic-pituitary-adrenal axis. As many as 80% of patients with a major depressive disorder have abnormally regulated cortisol secretion. Typically, circadian changes in ACTH and cortisol secretion are maintained, but ACTH pulse frequencies are increased and the resultant cortisol secretion is of greater magnitude. These biochemical abnormalities often produce a mildly elevated serum cortisol concentration, usually less than three times the upper limit of the normal range, which varies with the severity of depression. With remission of depression, the hypercortisolism is also reversed.

Alcoholism. Chronic alcoholism also is a cause of pseudo-Cushing’s syndrome. Although not fully understood, the hormone abnormalities appear to be due to increased hypothalamic secretion of CRH, impaired hepatic metabolism of cortisol, or both. Almost uniformly, these patients also have elevated serum concentrations of hepatic enzymes. With abstinence from alcohol, these hormone abnormalities rapidly disappear.

Other causes. Finally, elevations of serum cortisol concentrations can be caused by severe illness, acute

Table 3. Causes of Pseudo-Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Major depressive disorders</th>
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<tbody>
<tr>
<td>Chronic alcoholism</td>
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<tr>
<td>Severe illness or stress</td>
</tr>
<tr>
<td>Major surgery/medical illness</td>
</tr>
<tr>
<td>Severe bacterial infection</td>
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<tr>
<td>Severe obesity (BMI &gt; 40 kg/m²)</td>
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<tr>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>Rapid weight loss/anorexia nervosa</td>
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<tr>
<td>Familial glucocorticoid resistance</td>
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BMI = body mass index.
stress (eg, due to major surgery), and rapid weight loss or anorexia nervosa. Also, a rare syndrome of familial glucocorticoid resistance may cause pseudo-Cushing’s syndrome. In this disorder, serum cortisol and ACTH concentrations are “set” to a higher level to compensate for a partial loss-of-function mutation in the glucocorticoid receptor. Physical features of Cushing’s syndrome are absent, although hypertension and hypokalemia due to excessive cortisol action on the type 1 mineralocorticoid receptor can occur. Signs and symptoms of adrenal androgen excess (secondary to ACTH stimulation) characterize the phenotype of the cortisol-resistant state in female patients.

**Recommended Diagnostic Approach**

A careful history and physical examination is required at the initial patient encounter. Most often, a clinical history of depression or alcohol use may be elicited, and the severity of these illnesses judged. Anorexic behavior should be suspected in the appropriate setting of weight loss and poor eating habits. A 24-hour UFC measurement greater than three times the upper limit of normal is highly suggestive of Cushing’s syndrome and almost always excludes pseudo-Cushing’s syndrome. Mild elevations of urinary cortisol in the appropriate clinical settings warrant further testing.

Depressed patients usually maintain normal circadian rhythms and a normal sensitivity to dexamethasone suppression, despite augmented cortisol secretion. As a result, a measurement of late night (11 PM to 1 AM) serum cortisol can be helpful, with values less than 5 µg/dL (140 nmol/L) confirming pseudo-Cushing’s syndrome.33 Similarly, a normal response to overnight dexamethasone suppression testing is supportive of pseudo-Cushing’s syndrome.

The diagnosis of chronic alcoholism is supported by typical hepatic enzyme elevations. Finally, glucocorticoid resistance syndrome, while exceedingly rare, should be considered when a familial pattern of excess serum cortisol is detected in patients in the absence of the usual signs and symptoms of hypercortisolism.

If the diagnosis remains in doubt, recent studies suggest that the combination of low-dose dexamethasone suppression and CRH stimulation testing is highly sensitive and specific for differentiating true Cushing’s from pseudo-Cushing’s syndrome. As noted, depressed patients have greater sensitivity to dexamethasone suppression, and patients with Cushing’s disease (ACTH-dependent cortisol excess) have greater plasma cortisol responses to exogenous CRH, thus providing the rationale for this test. Dexamethasone (0.5 mg) is administered eight times every 6 hours over 2 days, beginning at 12 noon on day 1. Following the final dose of dexamethasone, a CRH stimulation test (1 µg/kg) is performed at 8 AM. A plasma cortisol concentration greater than 1.4 µg/dL measured 15 minutes after the administration of CRH correctly identifies patients with Cushing’s syndrome and excludes those with pseudo-Cushing’s syndrome.34

**CASE RESOLUTION**

The patient’s history of depression and findings on cortisol testing prompt the endocrinologist to suspect pseudo-Cushing’s syndrome. To confirm this diagnosis, the patient undergoes combined low-dose dexamethasone suppression and CRH stimulation testing. At 15 minutes after CRH stimulation, her plasma cortisol concentration is 0.7 µg/dL. A repeat 24-hour UFC measurement is taken 6 months later, when the patient’s depression is in remission, and is found to be normal.

**REFERENCES**

Cushing’s Syndrome


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