CUSHING’S SYNDROME

Case: A 43-year-old man with delusions

A previously healthy 43-year-old man is brought to the emergency department for evaluation of confusion. The patient has complained to his wife of weight gain and frequent urination for the past several months. Over the same period, he has had progressive weakness in his shoulders and legs, recently requiring help to rise from a seated position. The patient’s wife became more concerned when he told her he is a secret agent of the Federal Bureau of Investigation. The patient has never smoked and does not drink alcohol or use illicit substances.

Heart rate is 110 beats per minute and blood pressure is 188/104 mm Hg. There are scattered ecchymoses, abdominal striae (Figure 8-1), and hyperpigmentation of the knuckles, palmar creases, and elbows. Proximal muscle weakness and atrophy are present.

Figure 8-1.

Serum glucose is 525 mg/dL and serum potassium is 2.1 mg/dL. Urine free cortisol is measured at 645 μg/day (reference range <50 μg/day). Plasma adrenocorticotropic hormone (ACTH) is 1000 pg/mL (reference range 10-60 pg/mL). Simultaneous sampling of the inferior petrosal sinus and peripheral blood is performed and reveals a central-to-peripheral ACTH concentration ratio of 0.6. Cross-sectional imaging of the chest reveals an endobronchial nodule within the left main bronchus (arrow, Figure 8-2).

Figure 8-2. (Courtesy of Cristina Fuss, MD.)

What is the most likely diagnosis in this patient?
What is Cushing’s syndrome? Cushing’s syndrome is a clinical condition that results from cortisol excess.

What is the normal hormonal cycle of the hypothalamic-pituitary-adrenal axis? The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the pituitary to secrete ACTH, which stimulates the adrenal glands to secrete cortisol, which then provides negative feedback to both the hypothalamus and pituitary (see Figure 7-2).\(^1\)

Are serum cortisol levels constant throughout the day? In healthy adults, secretion of cortisol is pulsatile and highest in the early morning.\(^2\)

What conditions normally stimulate the hypothalamus to secrete corticotropin-releasing hormone? Stimulants of CRH secretion include stress (eg, trauma, surgery, infection), psychiatric disturbance (eg, depression, anxiety), sleep-wake transition, and low serum cortisol.\(^1\)

How common is Cushing’s syndrome? Cushing’s syndrome is present in up to 8 per 100,000 persons in the general population. It is estimated that an equal number of cases are undiagnosed. The median age of diagnosis is 40 years with a 3:1 female-to-male predominance.

What are the clinical manifestations of Cushing’s syndrome? Clinical manifestations of Cushing’s syndrome (Figure 8-3) may include central obesity, “moon facies” (rounded face due to fat deposition), “buffalo hump” (increased fat deposition between the shoulders), thin skin, bruising, abdominal striae, hyperpigmentation (ACTH-dependent causes only), hirsutism, oligomenorrhea, psychosis, proximal myopathy, arterial hypertension, polycythemia, hyperglycemia (with associated polyuria), hypokalemia, and osteopenia. The manifestations of hypercortisolism can generally be divided into anabolic (eg, polycythemia) and antianabolic effects (eg, thin skin).\(^3\)

What condition, which is on the rise in the industrialized world, is often confused for Cushing’s syndrome? The metabolic syndrome of obesity is associated with the same anabolic signs as the syndrome of glucocorticoid excess. A focus on the antianabolic effects of cortisol excess is useful for differentiating Cushing’s syndrome from simple obesity. The probability of Cushing’s syndrome exceeds 90% in the obese population when the triad of thin skin (established when a skin fold over the proximal phalanx of the middle finger of the nondominant hand is <2 mm thick), osteoporosis, and ecchymoses is present.\(^3\)

If Cushing’s syndrome is suspected based on the clinical evaluation, what is the next diagnostic step? In patients with a clinical condition compatible with Cushing’s syndrome, a confirmatory laboratory test should be obtained. When carefully performed, the urine free cortisol (UFC) test, which measures the quantity of free cortisol secreted in the urine in a 24-hour period, is the most reliable confirmatory test. The upper limit of the normal reference range for this test should be increased slightly in patients with depression. When renal function is abnormal, UFC is less reliable. In such patients, confirmatory tests of salivary cortisol may be helpful.\(^3,4\)
What are the possible explanations for patients who have a clinical condition compatible with Cushing’s syndrome but a negative confirmatory test?

If Cushing’s syndrome is present clinically, then a negative confirmatory test (ie, UFC is not elevated) indicates either exposure to exogenous glucocorticoids or a false-negative confirmatory study.1

In patients with Cushing’s syndrome related to exogenous glucocorticoids, what are the dangers of abrupt glucocorticoid cessation?

In patients with Cushing’s syndrome related to exogenous glucocorticoids, the danger of abrupt glucocorticoid cessation is twofold. First, recrudescence of the underlying condition being treated (eg, rheumatoid arthritis) may occur. Second, chronic exposure to supraphysiological levels of glucocorticoids can lead to the development of central adrenal insufficiency, which will become unmasked if glucocorticoids are stopped abruptly. For these reasons, it is preferred that exogenous glucocorticoids are tapered over a period of time.

How can exogenous glucocorticoids be discontinued safely?

Exogenous glucocorticoids can be safely and efficiently discontinued using the following strategy: (1) reduce the glucocorticoid to physiologic dose (10-12 mg/m² per day of hydrocortisone or equivalent); (2) obtain an ACTH stimulation test (before the morning dose of glucocorticoid) every 3 months; (3) stop all glucocorticoids when there is an adequate response to the ACTH stimulation test (ie, cortisol levels rise to ≥18 µg/dL). The hypothalamic-pituitary-adrenal axis eventually recovers in the vast majority of patients.5

What strategies can minimize the risk of a false-negative urine free cortisol test?

To minimize the chance of a false-negative result, UFC samples must be complete (ie, all urine must be collected over a full 24-hour period) and measured with high-performance liquid chromatography and mass spectrometry in patients with normal renal function. The most reliable way to confirm that a complete 24-hour urine collection has been obtained is to measure urinary creatinine. Urinary creatinine <1.5 g per day for men and <1.0 g per day for women indicates incomplete collection, and the test should be repeated.3

If the confirmatory test is positive, what is the next diagnostic step in the evaluation of Cushing’s syndrome?

In a patient with a clinical condition compatible with Cushing’s syndrome, a positive confirmatory test (ie, UFC is elevated) should prompt measurement of plasma ACTH levels. The plasma ACTH level determines whether Cushing’s syndrome is ACTH-dependent (ACTH level is elevated or normal) or ACTH-independent (ACTH level is low).
In the setting of cortisol excess, why does a normal plasma ACTH value imply an ACTH-dependent process?

In patients with ACTH-dependent Cushing’s syndrome, what is the next diagnostic step in evaluation?

What is the relative prevalence of ACTH-dependent and ACTH-independent causes of Cushing’s syndrome?

ACTH-dependent causes of Cushing’s syndrome represent 80% of cases, whereas ACTH-independent causes make up the remaining 20%.

ACTH-dependent Cushing’s syndrome

What is the fundamental mechanism of hypercortisolism in patients with ACTH-dependent Cushing’s syndrome?

Patients with ACTH-dependent Cushing’s syndrome should undergo inferior petrosal sinus sampling to determine if the excess ACTH is eutopic (from the pituitary gland) or ectopic (from elsewhere). Following direct stimulation of the pituitary gland with CRH, ACTH plasma levels from the inferior petrosal sinus and periphery (eg, antecubital vein) are simultaneously measured. Eutopic ACTH secretion is associated with a central-to-peripheral ACTH ratio ≥3. Ectopic ACTH secretion is associated with a central-to-peripheral ACTH ratio <3.

Cushing’s syndrome caused by eutopic ACTH production

What are the causes of eutopic ACTH production?

When caused by this underlying condition, Cushing’s syndrome is known as “Cushing’s disease.”

- Pituitary adenoma.
- Excess CRH.
- The pituitary is overstimulated.
What are the characteristics of ACTH-secreting pituitary adenomas?

**Pituitary adenoma** is the most common cause of ACTH-dependent Cushing’s syndrome, about 7 times more common than ectopic sources of ACTH. It is more common in women by a ratio of 4:1, with a peak incidence in the third and fourth decades of life. About half of ACTH-secreting pituitary adenomas are visible on magnetic resonance imaging (MRI) of the brain (Figure 8-4). Transsphenoidal adenectomy is the initial treatment of choice for Cushing’s disease. If successful, the plasma cortisol level on the morning after transsphenoidal adenectomy will be zero. Glucocorticoid replacement is necessary until the hypothalamic-pituitary-adrenal axis regains function, which typically takes a year or longer. Up to one-third of patients will eventually experience a recurrence.3,6

What are the sources of excess corticotropin-releasing hormone?

Excess CRH can be caused by pseudo-Cushing’s syndrome or ectopic CRH production from a tumor (rare).

What is the most common cause of pseudo-Cushing’s syndrome?

Chronic alcohol use is the most common cause of pseudo-Cushing’s syndrome. Investigation into the possibility of alcohol-induced pseudo-Cushing’s syndrome begins with a period of abstinence from alcohol, followed by clinical monitoring.3

**CUSHING'S SYNDROME CAUSED BY ECTOPIC ACTH PRODUCTION**

What electrolyte disturbance is associated with Cushing’s syndrome caused by ectopic ACTH production?

Hypokalemia is present in the majority of patients with Cushing’s syndrome related to ectopic ACTH production but is only rarely seen in patients with Cushing’s disease. This observation has several explanations. First, compared with those with Cushing’s disease, patients with ectopic ACTH production generally have higher circulating levels of cortisol, which has activity at the mineralocorticoid receptor (which, when activated, promotes renal potassium excretion). Second, the activity of 11β-hydroxysteroid dehydrogenase type 2, which is essential in preventing the mineralocorticoid activity of cortisol, is decreased in patients with ectopic ACTH production.7
What are the causes of ectopic ACTH production?

Smoking is the most important risk factor for the development of this malignancy.

This neuroendocrine tumor, when located in the gastrointestinal tract, can be associated with flushing and diarrhea.

A pancreatic mass is identified on cross-sectional imaging in a patient with Cushing’s syndrome.

A type of thyroid cancer that originates from the parafollicular cells (C cells).

A 32-year-old man presents with episodes of headache, chest pressure, tachycardia, and hypertension.

What are the characteristics of Cushing’s syndrome related to small cell lung cancer?

Patients with ectopic ACTH production from small cell lung cancer are more likely to present with weight loss, hypokalemia, abnormal glucose tolerance, and edema rather than the more classic manifestations of Cushing’s syndrome. In addition to ectopic ACTH production, small cell lung cancer can cause other paraneoplastic endocrine syndromes, including the syndrome of inappropriate antidiuretic hormone (SIADH), and hypercalcemia via parathyroid hormone–related peptide (PTHrP). Treatment of Cushing’s syndrome related to small cell lung cancer includes radical excision of the tumor, chemotherapy, and pharmacologic cortisol inhibition (eg, ketoconazole). Prognosis is poor.

What are the most common locations of carcinoid tumors associated with ectopic production of ACTH?

Carcinoid tumors of the lung, thymus, and pancreas are most often associated with ectopic ACTH production. Thymic carcinoid tumors in particular are associated with poor prognosis.
What are the characteristics of pancreatic islet cell tumors that secrete ACTH?

Pancreatic islet cell tumors account for up to 3% of pancreatic tumors. These tumors are capable of secreting various hormones, including insulin, gastrin, glucagon, and ACTH. When the tumor is limited to the pancreas, secreted ACTH enters the enterohepatic circulation and is rapidly metabolized by the liver, preventing the clinical syndrome from developing. By the time Cushing’s syndrome has become apparent, most ACTH-secreting pancreatic islet cell tumors are advanced, with hepatic metastases, and are associated with poor prognosis.

Which genetic syndrome is associated with the development of both medullary thyroid carcinoma and pheochromocytoma?

Medullary thyroid carcinoma and pheochromocytoma can occur together in multiple endocrine neoplasia types 2a and 2b but are most often sporadic. These entities are relatively rare sources of ectopic ACTH production.

In patients with Cushing’s syndrome caused by ectopic ACTH production, what is the next diagnostic step?

Patients with ectopic sources of ACTH production should undergo an imaging study guided by the clinical presentation (eg, a patient with a history and examination compatible with pheochromocytoma should undergo imaging of the adrenal glands). When there are no clinical clues to a possible tumor site, patients should first undergo computed tomography imaging or MRI of the chest; a tumor will be found in the majority of patients. If a tumor is not identified in the chest, then MRI of the abdomen and pelvis should be performed next.

If the source of ectopic ACTH production cannot be identified after imaging the chest, abdomen, and pelvis, what treatment options are available?

If a tumor cannot be identified in patients with ectopic ACTH production, there are 2 options for management: pharmacologic blockade of cortisol synthesis or bilateral adrenalectomy.

ACTH-INDEPENDENT CUSHING’S SYNDROME

What is the fundamental mechanism of hypercortisolism in patients with ACTH-independent Cushing’s syndrome?

ACTH-independent Cushing’s syndrome occurs as a result of excess cortisol production by the adrenal glands, independent of ACTH stimulation.

What are the ACTH-independent causes of Cushing’s syndrome?

Cross-sectional imaging of the adrenal glands can be helpful in distinguishing these 2 causes of ACTH-independent Cushing’s syndrome.

Adrenal tumor and adrenal hyperplasia.

**Cushing’s syndrome**

- Confirmatory test

  - Negative
    - Exogenous glucocorticoids
    - False-negative study
  - Positive
    - ACTH-dependent
      - Eutopic
        - Pituitary adenoma
        - Excess corticotropin-releasing hormone
      - Ectopic
        - Small cell lung cancer
        - Carcinoid tumor
        - Pancreatic islet cell tumor
        - Medullary thyroid carcinoma
        - Pheochromocytoma
    - ACTH-independent
      - Adrenal tumor
      - Adrenal hyperplasia
What are the characteristics of adrenal tumors that cause Cushing’s syndrome?

Adrenal tumors capable of causing Cushing’s syndrome via secretion of excess cortisol include both adenomas (benign) and carcinomas (malignant). Benign tumors tend to be smaller in size (<5 cm) and secrete only 1 hormone (eg, cortisol). These tumors are treated with laparoscopic adrenalectomy with a high rate of success. Malignant tumors tend to be larger in size (>5 cm) and secrete more than 1 hormone (eg, cortisol and androgen). Surgical removal of all detectable tissue, including metastases, should be pursued.

What are the 2 general types of ACTH-independent adrenal hyperplasia?

Cushing’s syndrome can occur as a result of micronodular adrenal hyperplasia or bilateral macronodular adrenal hyperplasia. These entities typically affect both adrenal glands. Bilateral adrenalectomy is curative. All patients who undergo bilateral adrenalectomy must be treated with lifelong glucocorticoid and mineralocorticoid replacement.

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**Case Summary**

A 43-year-old man presents with weight gain, polyuria, and confusion, and is found to have ecchymoses, abdominal striae, and hyperpigmentation on examination and an endobronchial nodule within the left main bronchus on cross-sectional imaging of the chest.

*What is the most likely diagnosis in this patient?*

Cushing’s syndrome related to ectopic ACTH production.

**BONUS QUESTIONS**

*Which clinical features in this case suggest the diagnosis of Cushing’s syndrome?*

Features of Cushing’s syndrome in this case include central obesity, psychosis, ecchymoses, abdominal striae (see Figure 8-1), polyuria (from hyperglycemia), arterial hypertension, proximal myopathy, hyperpigmentation, and hypokalemia.

*What is the significance of the hyperpigmentation in this case?*

Hyperpigmentation is associated only with ACTH-dependent Cushing’s syndrome. High levels of ACTH stimulate the melanocortin-1 receptor in the skin, resulting in hyperpigmentation. It tends to first occur in areas of the skin under pressure, including elbows, knuckles, palmar creases, lips, and buccal mucosa.

*What is the most likely cause of Cushing’s syndrome in this case?*

The patient in this case has ACTH-dependent Cushing’s syndrome based on the elevated plasma ACTH level. Inferior petrosal sinus sampling demonstrates a central-to-peripheral ACTH ratio <3, implying an ectopic source of ACTH production. In such patients, cross-sectional imaging of the chest often reveals the source. In this case, the endobronchial nodule within the left main bronchus (see Figure 8-2, arrow) is most likely a bronchial carcinoid tumor. Bronchoscopy with biopsy would confirm the diagnosis.

*What other type of lung cancer is associated with ectopic ACTH production?*

Cushing’s syndrome can also occur in patients with small cell lung cancer. However, these patients are less likely to present with the classic manifestations of Cushing’s syndrome. Bronchial carcinoid tumors tend to follow a more chronic and indolent course, which allows for full development of Cushing’s syndrome.

*What is the treatment of choice for Cushing’s syndrome related to ectopic ACTH production?*

Cushing’s syndrome related to ectopic ACTH production should be treated with surgical removal of the tumor if it can be located. If surgery is not possible or the tumor cannot be located, other treatment options include pharmacologic cortisol synthesis blockade (eg, ketoconazole), and bilateral adrenalectomy.
KEY POINTS

- Cushing’s syndrome is a clinical condition that results from cortisol excess.

- Clinical manifestations of Cushing’s syndrome include central obesity, moon facies, buffalo hump, thin skin, bruising, abdominal striae, hyperpigmentation, hirsutism, oligomenorrhea, psychosis, proximal myopathy, arterial hypertension, hyperglycemia, hypokalemia, and osteopenia.

- When Cushing’s syndrome is suspected clinically, it should be confirmed with the UFC test.

- If the UFC test is negative, it may be a false-negative result or the patient may be receiving exogenous glucocorticoids.

- Plasma ACTH level determines whether Cushing’s syndrome is ACTH-dependent (80% of cases) or ACTH-independent (20% of cases).

- ACTH-dependent Cushing’s syndrome occurs as a result of eutopic (pituitary) or ectopic ACTH excess. Inferior petrosal sinus sampling is used to distinguish eutopic and ectopic sources of ACTH production.

- ACTH-independent Cushing’s syndrome occurs as a result of cortisol excess from the adrenal gland(s).

- Treatment for Cushing’s syndrome may involve surgical and pharmacologic modalities, depending on the underlying cause.

REFERENCES