Cushing Syndrome: Diagnostic Workup and Imaging Features, With Clinical and Pathologic Correlation

**OBJECTIVE.** Cushing syndrome (CS) is a constellation of clinical signs and symptoms resulting from chronic exposure to excess cortisol, either exogenous or endogenous. Exogenous CS is most commonly caused by administration of glucocorticoids. Endogenous CS is subdivided into two types: adrenocorticotrophic hormone (ACTH) dependent and ACTH independent.

**CONCLUSION.** Cushing disease, which is caused by a pituitary adenoma, is the most common cause of ACTH-dependent CS for which pituitary MRI can be diagnostic, with bilateral inferior petrosal sinus sampling useful in equivocal cases. In ectopic ACTH production, which is usually caused by a tumor in the thorax (e.g., small cell lung carcinoma, bronchial and thymic carcinoids, or medullary thyroid carcinoma) or abdomen (e.g., gastroenteropancreatic neuroendocrine tumors or pheochromocytoma), CT, MRI, and nuclear medicine tests are used for localizing the source of ACTH. In ACTH-independent CS, which is caused by various adrenal abnormalities, adrenal protocol CT or MRI is usually diagnostic.

**HISTORY.**

Cushing W. Cushing, known as the father of modern neurosurgery, first described in the early part of the 20th century an endocrinologic syndrome of hypercortisolism caused by a malfunction of the pituitary gland, which he termed "polyglandular syndrome."[1] This condition, now eponymously termed Cushing disease, represents a state of excessive cortisol levels due to a pituitary adenoma[1–3]. Cushing syndrome (CS), in contradistinction, represents hypercortisolism stemming from various causes other than a pituitary adenoma.

The purpose of this article is to review the clinical features and diagnosis of CS, the imaging localization of the source of hypercortisolism, and the management of CS.

**Normal Hypothalamic-Pituitary-Adrenal Axis Function**

Cortisol, a glucocorticoid steroid hormone that is produced in the zona fasciculata of the adrenal cortex, is essential to the maintenance of homeostasis in the presence of stressors[4]. It is derived from cholesterol through a series of enzymatic reactions. Physical and psychologic stressors are the main stimuli for corticotropin-releasing hormone (CRH) secretion from the hypothalamus. CRH transported via the hypothalamic-pituitary tract induces the corticotrophs in the anterior lobe of the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the systemic circulation, which, in turn, stimulates the zona fasciculata of the adrenal cortex to synthesize and secrete glucocorticoids[4]. Cortisol affects a variety of systems and organs, including the immune system (e.g., antiinflammatory and immunosuppressive processes), liver (e.g., gluconeogenesis), kidneys (e.g., electrolyte and water balance), stomach (e.g., increased gastric-acid secretion), and bones (e.g., reduced bone formation).

The level of cortisol in blood is controlled through its negative feedback on hypothalamic-pituitary-adrenal axis activation, both at the level of the hypothalamus (decreased CRH secretion) and pituitary gland (decreased ACTH secretion)[4]. Cortisol is metabolized in the liver, and its metabolites are excreted in the urine[5]. CS is caused by prolonged exposure to excess cortisol and represents a constellation of clinical signs and symptoms.

**Epidemiology**

Endogenous CS is an uncommon disorder, with population-based studies showing an incidence of 0.7–2.4 cases per million population per year[6,7]. The female-to-male ratio

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**Keywords:** adrenal adenoma, adrenocortical carcinoma, adrenocorticotrophic hormone–independent macromodular adrenal hyperplasia, Cushing disease, Cushing syndrome, pituitary adenoma, primary pigmented nodular adrenal disease

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TABLE 1: Clinical Features of Cushing Syndrome

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
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<tbody>
<tr>
<td>Body fat</td>
<td>Central obesity (Fig. 1A); fat accumulation in trunk, supraclavicular, and dorsocervical regions (i.e., buffalo hump), and around face (i.e., moon facies); mediastinal lipomatosis</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Skin thinning and friability; disruption and weakness of the subcutaneous collagenous tissue leading to multiple red-purple striae &gt; 1 cm in width mainly along the abdomen (Fig. 1B) but also occurring anywhere there is rapid skin expansion (Fig. 1C); easy bruising; poor wound healing; hyperpigmentation (adrenocorticotropic hormone–dependent Cushing syndrome); hirsutism; frontal balding; acne</td>
</tr>
<tr>
<td>Muscle</td>
<td>Proximal muscle weakness; wasting of the extremities; reduced muscle volume</td>
</tr>
<tr>
<td>Bones</td>
<td>Osteoporosis; osteoporotic spine fractures (Fig. 1D); rib, metatarsal, wrist, and hip fractures; avascular necrosis of the femoral heads (Fig. 1E)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension; stroke; myocardial infarction; thromboembolic disease</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Type 2 diabetes mellitus; increased hepatic glycogen production; dyslipidemia; alkalosis; hypokalemia</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Menstrual abnormalities and amenorrhea in female patients; decreased libido and sexual dysfunction in male patients; infertility</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Depression; emotional liability; lethargy; anxiety; insomnia; memory and cognitive changes</td>
</tr>
<tr>
<td>Immune system</td>
<td>Impaired immune function; recurrent infections</td>
</tr>
</tbody>
</table>

Note—Table was created using data published elsewhere [13–15, 19–21].

is 3:1 except for the subtype of ectopic ACTH syndrome, which is equally common in male patients [3, 8, 9]. Subclinical CS refers to the presence of autonomous mild cortisol hypersecretion in a patient who lacks the classic or overt signs of CS and is present in 5–20% of patients with an incidental finding of an adrenal mass (adrenal incidentaloma) [10–12].

**Clinical Features of Cushing Syndrome**

Clinical manifestations of CS depend on the patient’s age and the duration and degree of the hypercortisolism [13–21] (Table 1 and Fig. 1). CS is associated with poor quality of life, morbidity, and a fivefold excess mortality [9, 14]. In florid cases, patients may present with central obesity with dorso cervical and supraclavicular fat accumulation, thinned skin with wide purple striae, fatigue, proximal muscle weakness, hypertension, glucose intolerance, acne, hirsutism, and menstrual irregularities [15]. Neuropsychological manifestations are frequent and include depression, sleep disturbances, emotional lability, and cognitive defects [15]. In children, growth retardation is frequently observed [15]. Because manifestations of CS are multiple and variable, the diagnosis may be challenging when signs and symptoms are subtle. A patient may therefore be treated for another systemic disease that has overlapping symptoms, such as diabetes mellitus or hypertension, without a definite diagnosis of CS. In clinical phenotypes of mild hypercortisolism, the clustering of multiple symptoms such as glucose intolerance and hypertension in the setting of recent weight gain, or the emergence of symptoms that are atypical for the patient’s age may point to the diagnosis [15]. Patients with subclinical CS have an increased incidence of hypertension, obesity, impaired glucose tolerance or diabetes mellitus, dyslipidemia, and osteoporosis but lack overt signs of hypercortisolism such as wide purple striae or proximal muscle weakness [10, 11].

**Classification of Cushing Syndrome**

CS can result from exogenous administration of glucocorticoids or endogenous overproduction of cortisol [16]. Endogenous CS is traditionally classified as ACTH-dependent, when pathologic ACTH secretion drives cortisol production, or as ACTH-independent, when the adrenal glands autonomously secrete excessive cortisol [7] (Table 2). The diagnosis of CS requires the confirmation of hypercortisolism, the differentiation between ACTH-dependent and ACTH-independent causes, and the differentiation between pituitary and ectopic sources of ACTH in ACTH-dependent CS [22].

**Exogenous Cushing Syndrome**

Exogenous or iatrogenic CS is more common than endogenous CS and results from the administration of supraphysiologic doses of glucocorticoids [7]. Exogenous administration of glucocorticoids is used to treat inflammatory, autoimmune, and neoplastic disorders [7]. Administration of synthetic ACTH is prescribed less often these days.

**Endogenous Cushing Syndrome: Adrenocorticotropic Hormone–Dependent Cushing Syndrome**

ACTH-dependent CS accounts for approximately 80% of the endogenous causes of CS, observed in 5% of cases [7]. ACTH-producing tumors are usually adenomas with 90% of cases occurring in males. A predominant clinical feature of this tumor is proptosis, which is a bulging of the eye and its surrounding tissue. ACTH secretion can lead to the development of Cushing syndrome, which is characterized by the presence of hyperglycemia, hypertension, and hyperlipidemia. This syndrome is often accompanied by increased appetite, weight gain, and acne. Other signs and symptoms may include facial edema, muscle weakness, and mood swings. Treatment involves surgical removal of the tumor, which can be performed using a minimally invasive approach. Additionally, medical therapy may be used to suppress ACTH production by the pituitary gland. This can be achieved through the use of a combination of hormones, such as dexamethasone and ketoconazole. Finally, radiotherapy may be used as an adjuvant therapy to reduce the size of the tumor or to prevent its recurrence.
and includes ACTH-secreting pituitary adenomas (Cushing disease), ectopic ACTH syndrome, and CRH-producing tumors [1].

Cushing disease—Cushing disease, which results from a pituitary adenoma producing ACTH, accounts for approximately 80% of cases of ACTH-dependent CS [7, 9] (Figs. 2 and 3). The ACTH-secreting pituitary adenoma stimulates the adrenal glands to secrete cortisol [2, 17]. Cushing disease typically occurs in the third or fourth decade of life, although children and young adolescents can also develop Cushing disease [18]. The frequency of Cushing disease is significantly higher among women.

Ectopic adrenocorticotropic hormone syndrome—Ectopic ACTH syndrome, which is due to ACTH production from nonpituitary tumors, accounts for approximately 20% of ACTH-dependent CS cases [3, 7, 9]. It is crucial to distinguish ectopic ACTH syndrome from the more common Cushing disease and to localize the source of ectopic ACTH secretion because surgical resection of the primary lesion has a high probability of cure, with complete remission in up to 80% of cases, and these extrapituitary tumors are frequently malignant [3, 23, 24]. Tumors of the lung are the most likely source of ectopic ACTH, with small cell lung cancer (Fig. 4) and bronchial carcinoid tumors (Fig. 5) accounting for approximately 50% of ectopic ACTH-secreting tumors [9, 23, 25]. Other causes of ectopic ACTH syndrome include nonlung neuroendocrine tumors (22.5%), including thymic (Fig. 6), pancreatic (Fig. 7), and gastrointestinal carcinoids; medullary thyroid carcinomas (7.5%); and phaeochromocytoma (2.5%) [9, 25].

Localization of the ectopic source of ACTH can be difficult and may be delayed for months to years, with consequent increased morbidity and mortality [26, 27]. In 12.5% of patients, the source of ectopic ACTH syndrome cannot be found, despite repeated clinical and imaging evaluations and long-term follow-up [23].

Corticotropin-releasing hormone-producing tumors—CS due to CRH-producing tumors is extremely rare, accounting for fewer than 1% of cases of ACTH-dependent CS [7]. In 20 cases reported in the literature, isolated CRH-producing tumors consisted of medullary thyroid carcinoma (33%), phaeochromocytoma (19%), carcinoma of the prostate (14%), small cell lung carcinoma (9.5%), and carcinoid (5%), with single cases of serous choristoma and gangliocytoma [27]. Although it is exceedingly rare, ectopic CRH syndrome should be included in the differential diagnosis for causes of CS [27].

Endogenous Cushing Syndrome: Adrenocorticotropic Hormone–Independent Cushing Syndrome

ACTH-independent CS, accounting for approximately 20% of all endogenous causes, results from autonomous secretion of cortisol from an adrenal gland lesion, usually an adenoma, adrenocortical carcinoma (ACC), or, very rarely, ACTH-independent macronodular adrenal hyperplasia or primary pigmented nodular adrenal disease (PPNAD) [9].

Adrenal adenoma—Adrenal adenomas are benign neoplasms of adrenocortical cells that account for approximately 60% of adrenal causes of CS [9, 28] (Fig. 8). Adrenal adenomas can be hormonally silent or they can produce clinical syndromes of hypercortisolism (CS), hyperaldosteronism, or, rarely, virilization or feminization. They are often discovered incidentally on abdominal imaging studies or may be sought when patients present with symptoms of hormonal excess.

Adrenocortical carcinoma—ACCs are rare often-aggressive tumors and account for approximately 40% of adrenal causes of CS [28] (Fig. 9). ACCs have an estimated annual incidence of two cases per million people with an estimated 5-year overall survival rate of 15–44% [28]. ACC tends to occur in the fourth or fifth decades of life and only extremely rarely in children [28]. ACC can occur sporadically or may be syndromic and associated with Li-Fraumeni syndrome, Lynch syndrome, familial adenomatous polyposis, or Beckwith-Wiedemann syndrome among others [28]. Up to 80% of children with ACC carry a germline TP53 mutation found in Li-Fraumeni syndrome [28]. Approximately 40% of ACCs are hormonally functioning and can secrete cortisol (most commonly), aldosterone, or androgens [28]. Functioning tumors are associated with increased morbidity and poorer survival compared with nonfunctioning tumors [28].

Primary pigmented nodular adrenal disease—PPNAD is a rare cause of ACTH-independent CS and accounts for fewer than 1% of adrenal causes of CS [3, 9] (Fig. 10). PPNAD is most frequently seen in infants, children, or young adults [29]. The clinical presentation may be atypical, with short stature, ashen body habitus, severe muscle wasting, and advanced osteoporosis commonly present [29, 30]. The majority of PPNAD cases are part of a Carney complex, characterized by cardiac and cutaneous myxomas, spotty skin pigmentation and lentigines, PPNAD, testicular tumors, and growth hormone–secreting pituitary tumors [29, 31, 32]. Carney complex arises from a mutation in the PRKARIA gene [9].

Adrenocorticotropic hormone–independent macronodular adrenal hyperplasia—ACTH-independent macronodular adrenal hyperplasia accounts for fewer than 1% of adrenal causes of CS [3, 9] (Fig. 11). ACTH-independent macronodular adrenal hyperplasia occurs equally in male as in female patients, in contrast to the predominantly female distribution of most cases of CS, and has a higher mean patient age compared with adenomas, Cushing disease, or PPNAD, most frequently presenting in the fifth to sixth decades of life [32, 33]. Most cases of ACTH-independent macronodular adrenal hyperplasia are sporadic, and patients may be identified either after an incidental imaging finding or during the workup of adrenal oversecretion syndrome [33]. Patients may have subclinical or overt CS [33].

Diagnostic Workup

Unless it is a florid case, CS can be challenging to diagnose owing to its variable clinical symptoms and signs, most of which are common in the general population [14]. When CS is clinically suspected, biochemical studies are needed to establish the presence of cortisol excess, before the cause of the excess cortisol is sought. The recommended screening tests include 24-hour urinary free cortisol, 1-mg overnight dexamethasone suppression, and late-night salivary cortisol level, which serve to confirm excess cortisol secretion in a 24-hour period, document the loss of feedback inhibition of cortisol on the hypothalamic-pituitary-adrenal axis, and document the loss of the normal diurnal variation of cortisol excretion, respectively [16] (Table 3).

Figure 12 provides a flowchart for the diagnosis and management of CS. After the diagnosis of CS is confirmed and the possibility of exogenous glucocorticoid administration is excluded, the next step is to determine whether excessive ACTH secretion is the cause. ACTH levels are measured to identify the subtype of CS, whether ACTH dependent or ACTH independent [6, 25, 34–36]. A normal or high ACTH level is consistent with ACTH-dependent CS (corticotroph adenoma in the pituitary gland or a tumor elsewhere as an
### TABLE 3: Biochemical Workup of Cushing Syndrome (CS)

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour urinary free cortisol</td>
<td>Measures level of free cortisol in the urine over a 24-hour period</td>
<td>Has 95% sensitivity and 98% specificity for diagnosing CS but needs to be repeated 2–3 times to optimize accuracy because there is significant variation in day-to-day cortisol excretion [17, 18, 72, 74]</td>
</tr>
<tr>
<td>Dexamethasone suppression test (DST)</td>
<td>Measures fasting plasma cortisol after administration of dexamethasone, which normally suppresses ACTH secretion, resulting in reduced cortisol production</td>
<td>Three normal urine collections can exclude CS</td>
</tr>
<tr>
<td>Late-night salivary cortisol</td>
<td>Detects elevated cortisol levels in the saliva between 11:00 pm and midnight</td>
<td>A threefold increase over normal cortisol levels is generally diagnostic of CS</td>
</tr>
<tr>
<td>ACTH measurement</td>
<td>Plasma ACTH levels are measured twice in the morning</td>
<td>Mild increase in urinary free cortisol is nonspecific</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH) stimulation test</td>
<td>ACTH and cortisol levels are measured at baseline and every 15 minutes after administration of CRH</td>
<td>There are two options for CS screening: 1-mg overnight DST and 2-day low-dose DST</td>
</tr>
<tr>
<td>Combined DST and CRH stimulation test</td>
<td>Dexamethasone is administered every 6 hours for 2 days followed by a CRH stimulation test; 24-hour urinary free cortisol levels are also checked at baseline and after dexamethasone administration</td>
<td>In CS, the normal circadian pattern of cortisol secretion is lost so the late night level no longer reaches nadir values; sensitivity and specificity in diagnosis are 86% and 100%, respectively [75, 76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distinguishes between ACTH-dependent and ACTH-independent CS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>An ACTH level &gt; 15 pg/mL is suggestive of ACTH-dependent CS, whereas a low ACTH level (&lt; 5 pg/mL) is seen in ACTH-independent CS [15, 25, 35, 36]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most cases with Cushing disease (about 85%) respond to CRH in the form of increased ACTH or cortisol, however, cases with ectopic ACTH secretion show no response [37]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differentiates between true CS and pseudo-CS</td>
</tr>
</tbody>
</table>

Note—Table was created using data published elsewhere [6, 16, 34]. ACTH = adrenocorticotropic hormone.

ectopic source of ACTH), because high cortisol levels would normally suppress ACTH. Abnormally low ACTH levels are consistent with ACTH-independent CS resulting from various adrenal abnormalities.

After the subtype of CS has been determined, imaging is the next step to identify the exact cause [22, 37, 38]. Pituitary MRI is an initial imaging study in ACTH-dependent CS to differentiate between pituitary and ectopic causes of ACTH production. If MRI shows a pituitary lesion compatible with an adenoma, then the pituitary lesion is the most likely source of excess ACTH. If the pituitary MRI is negative or the initial biochemical workup is inconclusive, then bilateral inferior petrosal sinus sampling, the reference standard for differentiating between pituitary and non-pituitary sources of ACTH, or a CRH stimulation test, is undertaken [9]. Pituitary adenomas causing Cushing disease usually respond to CRH stimulation, whereas ectopic ACTH-secreting tumors do not, thereby enabling differentiation with the CRH stimulation test [39].

In the workup of patients with an adrenal incidentaloma who do not have overt clinical signs of CS, there is no consensus on the algorithm for establishing the diagnosis of subclinical CS, but inadequate suppression of cortisol in response to a 1-mg overnight dexamethasone suppression test is most commonly present [10]. In patients with bilateral adrenal masses and clinical or subclinical CS, adrenal venous sampling may accurately determine whether cortisol hypersecretion is unilateral or bilateral, which is critical when treatment with adrenalectomy is considered [12, 40–42].

### Imaging Evaluation of Cushing Syndrome

**Adrenocorticotropic Hormone–Dependent Cushing Syndrome**

**Pituitary MRI**—Once the diagnosis of ACTH-dependent CS is confirmed, a high-resolution pituitary MRI with gadolinium-based contrast agent should be performed for all patients [15]; this is used to confirm the presence or absence of a pituitary lesion and to differentiate the source of ACTH between pituitary adenomas and ectopic lesions. MRI provides high soft-tissue contrast and anatomic detail and multidetector imaging capability, without ionizing radiation. After IV injection of the gadolinium-based contrast agent, thin-section (2 or 3 mm) T1-weighted spin-echo coronal images are acquired through the sella turcica at 10-second intervals. Compared with standard contrast-enhanced T1-weighted spin-echo techniques, spoiled gradient recalled acquisition in the steady state allows greater spatial resolution and superior sensitivity for detection of pituitary adenomas, but at the expense of a slightly higher false-positive rate [43]. Volume interpolated 3D spoiled gradient-echo MRI sequences have been shown to improve localization of pituitary microadenomas compared with dynamic contrast-enhanced spin-echo MRI sequences, particularly when the dynamic contrast-enhanced spin-echo MRI sequence is negative or equivocal [44].

MRI reveals a discrete pituitary adenoma in up to 60% of patients with ACTH-dependent CS [15] (Figs. 2 and 3). A pituitary adenoma is usually a microadenoma, defined as smaller than 10 mm in the longest dimension, with a mean size detected by MRI of 6 mm. It should be noted, however, that MR images may be interpreted
as normal in up to 40–50% of patients with documented ACTH-secreting pituitary adenomas because of the small size of these adenomas [16]. Dynamic contrast-enhanced pituitary MRI improves detection relative to unenhanced MRI; however, not all potential adenomas will be identified [16]. At MRI, a pituitary adenoma appears as a focal hypoenhancing nodule in the early dynamic phase compared with the surrounding homogeneously enhanced gland [6]. A potential pitfall is that small, usually less than 5 mm in diameter, focal lesions mimicking microadenomas may be noted incidentally at MRI in 10% of the population, and so additional imaging is needed to clarify whether the source of ACTH is in the pituitary gland [15, 16]. Further tests include bilateral inferior petrosal sinus sampling, which can confirm the pituitary gland as the source of ACTH excess or additional biochemical testing (e.g., CRH stimulation test) [6, 15]. When a pituitary macroadenoma (>10 mm) is present, normal glandular tissue may be difficult to detect; in these cases, any mass effect on the surrounding structures (e.g., the optic chiasm and cavernous sinus) should be assessed. CT is not used for first-line assessment of the pituitary gland owing to its lower sensitivity relative to MRI but can be used when MRI is contraindicated, such as when an aneurysm clip is present.

Bilateral inferior petrosal sinus sampling—Because transphenoidal surgery is widely accepted as the primary treatment option for pituitary adenoma, bilateral inferior petrosal sinus sampling, with its high sensitivity (95–99%) and specificity for Cushing disease and a diagnostic accuracy of more than 90%, is performed as the reference standard to confirm the pituitary gland as the source of excess ACTH and to help exclude an ectopic source of ACTH [15, 45, 46]. Bilateral inferior petrosal sinus sampling should be pursued in patients with ACTH-dependent CS whose clinical, biochemical, or radiologic results are equivocal or discordant [15]. Bilateral inferior petrosal sinus sampling should be performed only in specialized centers by an experienced radiologist because of its potential for significant complications, including vascular damage to the brainstem, deep venous thrombosis, pulmonary emboli, and cranial nerve palsies [15, 45, 47, 48]. The procedure should be performed during active secretion of ACTH by the tumor, which can be determined by elevated levels of measured cortisol [15]. After the radiologist catheterizes both inferior petrosal sinuses, blood samples for ACTH measurements are collected from both sides simultaneously, with another sample from a peripheral vein in the basal state and at subsequent timed intervals (i.e., 3, 5, and 10 minutes) after IV injection of CRH (100 µg) [15, 45, 48].

An inferior petrosal sinus-to-peripheral ACTH ratio greater than 2.0 in the basal state or greater than 3.0 after injection of CRH is diagnostic of Cushing disease [15]. Lower inferior petrosal sinus-to-peripheral ACTH ratios are highly suggestive of an ectopic ACTH-secreting tumor, with a specificity of 95–99% [15, 45, 47, 48].

Ectopic Adrenocorticotropic Hormone–Secreting Tumors

Thoracic sources of ectopic adrenocorticotropic hormone—When Cushing disease has been excluded by pituitary MRI or bilateral inferior petrosal sinus sampling, in the case of ACTH-dependent CS, the ectopic source of the ACTH is sought. Contrast-enhanced CT of the chest is the next study obtained to assess for intrathoracic tumors that could be the source of ACTH because the chest is the most common body region for ectopic ACTH-secreting tumors [6, 26, 49]. Small cell carcinoma of the lung (Fig. 4) represents approximately 20–50% of these cases. Other thoracic tumors, such as bronchial (Fig. 5) and thymic (Fig. 6) carcinoids, as well as medullary thyroid carcinoma, may also secrete ACTH. Localization of the ectopic source of ACTH can be difficult and may be delayed for months to years, with resultant increased morbidity and mortality. Several reports have described the usefulness of selective pulmonary arteri al sampling with ACTH measurement for localizing and confirming ectopic ACTH production by small bronchial carcinoid tumors when the diagnosis could not be confirmed by noninvasive modalities, including somatostatin receptor scintigraphy or $^{18}$F-FDG PET [50–52]. Although MRI has limited value in detection of bronchial carcinoids in the chest, it could be valuable in diagnosing mediastinal lesions such as thymic tumors.

Abdominal sources of ectopic adrenocorticotropic hormone—After exclusion of more common intrathoracic sources of ACTH-secreting tumors, CT or MRI scan of the abdomen is performed to evaluate for intraabdominal ACTH-secreting neoplasms. These tumors include gastroenteropancreatic neuroendocrine tumors, most commonly islet cell tumors of the pancreas and gastrointestinal carcinoids, and pheochromocytomas [6, 15, 26]. Islet cell tumors of the pancreas are usually small and intensely enhancing in the early arterial phase, and a specific diagnosis is suggested by the tumor markers and hormonal profile. Intestinal carcinoid tumors are suspected when a calcified mesenteric mass is seen, often with associated mesenteric fibrotic changes. These tumors may be associated with vascular compromise and mesenteric ischemia [26].

If one of these modalities fails to detect the ectopic focus, multiple imaging techniques (e.g., MRI plus octreotide scan or PET scan of the whole body) should be applied to localize the ectopic source of ACTH [6, 26]. Selective venous sampling may help localize occult endocrine tumors and includes systemic and transhepatic intestinal, pancreatic, and portal venous sampling. Some cases may need image-guided biopsy confirmation when surgical planning is requested [53, 54].

Nuclear Medicine Tests

Nuclear medicine functional imaging tests, including octreotide scan, FDG PET, and $^{68}$Ga-somatostatin receptor PET/CT, improve the sensitivity of conventional CT and MRI when hormone-secreting tumors in CS prove difficult to detect [24]. Molecular imaging can detect approximately 80% of tumors unidentified by conventional radiology [24].

Octreotide Scan ($^{111}$In-Pentetreotide Scintigraphy)

Octreotide scan, or octreoscan (Figs. 5, 6B, and 7B), is a scintigraphy test that can be used to detect occult ACTH-secreting neuroendocrine tumors when CT and MRI fail to identify the source of ACTH [23]. Octreotide is a synthetic somatostatin analog, and its diethylamidinepentaaacetic acid conjugate, pentetreotide, is labeled with $^{111}$In and injected IV. The pentetreotide binds to somatostatin receptors (subtypes 2 and 5) present on the cell membranes of many types of neuroendocrine tumor cells. Octreotide scan can be used to localize gastroenteropancreatic neuroendocrine tumors (e.g., intestinal carcinoids), adrenal medullary tumors (e.g., pheochromocytomas), bronchial carcinoids, and small cell lung carcinoma.

Gallium-68 Somatostatin Receptor PET/CT

Somatostatin-analogs radiolabeled with $^{68}$Ga for PET are useful for detecting ectopic ACTH-secreting tumors and offer higher spatial resolution and improved pharmacokinetics compared with somatostatin-analog scintigraphy [55, 56]. Gallium-68 somatostatin
receptor PET/CT, which includes $^{68}$Ga-1, 4, 7, 10-tetraazacyclododecan-1-4, 7, 10-tetraacetic acid (DOTA)-(Tyr$^3$)-octreotate, $^{68}$Ga-DOTATOC (Tyr$^3$)-octreotide, and $^{68}$Ga-DOTATATE-1-Nal$^3$-octreotide, shows the highest sensitivity among molecular imaging tests for detecting neuroendocrine tumors in ectopic CS [24, 57].

**Imaging for Adrenocorticotropic Hormone–Independent Cushing Syndrome**

**Adrenal CT or MRI**

Adrenal imaging studies are not needed for patients who have ACTH-dependent CS but are required for those with ACTH-independent CS [16]. CT is the optimal non-invasive imaging modality for diagnosing adrenal lesions in ACTH-independent CS because adrenal adenoma, carcinoma, and ACTH-independent macronodular adrenal hyperplasia are invariably detectable by CT [9, 54]. An adrenal CT should be performed with thin (2.5- to 3-mm) CT slices before and after the IV administration of 100–150 mL of iodinated contrast material. MDCT scanners with 1-mm or smaller collimation and multiplanar reconstruction capabilities allow excellent delineation of adrenal anatomy and the anatomic relationship of an adrenal lesion [58]. At CT, normal adrenal glands appear homogeneous and symmetric with soft-tissue attenuation similar to that of the kidney [54, 58]. Adrenal MRI can provide a similar assessment as CT.

**Adrenal Adenoma**

Adrenal adenomas are usually well-defined ovoid or round nodules that are relatively small, typically measuring 1–5 cm, with homogeneous or slightly heterogeneous attenuation [32] (Fig. 8). Unfortunately, the imaging features at CT of hyperfunctioning cortisol-producing adenomas that cause CS overlap with those of incidental nonfunctioning adenomas; therefore, they cannot be distinguished from one another by conventional imaging alone, but can be differentiated by adrenal venous sampling [12, 32, 40, 42, 58].

Approximately 70% of adrenal adenomas are lipid rich, containing abundant intracellular lipid (cholesterol, fatty acids, and neutral fat), in contrast to the vast majority of malignant lesions that do not [59]. The intracellular lipid content of most adenomas lowers the CT attenuation of the lesion, allowing them to be differentiated from nonadenomas at unenhanced CT when an ROI drawn over the nodule has attenuation measuring less than 10 HU [59]. This threshold value of 10 HU shows a very high specificity of 98% and a sensitivity of 71% [60]. Larger adenomas, usually greater than 3 cm, may exhibit heterogeneous attenuation with internal areas of hemorrhage and liquefaction [61]. Approximately 30% of adrenal adenomas are lipid poor and have attenuation values greater than 10 HU on unenhanced CT images, similar to the majority of malignant lesions [58, 59]. Therefore, a lesion with an unenhanced CT attenuation of greater than 10 HU necessitates further evaluation, such as CT washout, to determine the cause [59].

IV contrast-enhanced CT of the adrenal glands is performed with two phases: the early phase occurs 1 minute after IV injection of contrast agent, and the delayed phase typically occurs 15 minutes after injection. Adrenal adenomas usually enhance rapidly but also de-enhance rapidly, which is known as contrast washout [59]. In comparison, malignant lesions show similar rapid enhancement but show slower contrast washout [59]. The ratio of the attenuation values of the lesion at the 15-minute delayed phase relative to the 1-minute early phase has been shown to accurately differentiate adenomas from nonadenomas [59].

The following equations are used to measure washout in an adrenal lesion on an adrenal CT image: absolute washout = 100% × (attenuation in early phase – attenuation in delayed phase) / (attenuation in early phase – unenhanced attenuation), and relative washout = 100% × (attenuation in early phase – attenuation in delayed phase) / attenuation in early phase. An absolute enhancement washout of more than 60% or a relative enhancement washout of more than 40% is diagnostic for adrenal adenoma with high sensitivity (> 86% for absolute washout and > 96% for relative washout) and high specificity (> 92% for absolute washout and 100% for relative washout) [59, 62].

MRI is useful in adrenal gland imaging owing to its inherent tissue-characterizing ability and chemical-shift imaging (CSI) capability, a crucial sequence of MRI evaluation of adrenal lesions [59]. Normal adrenal glands exhibit low to intermediate signal at T1-weighted imaging and similar or slightly lower signal at T2-weighted imaging compared with the liver [54, 58]. Adenomas usually appear as well-defined, round, or ovoid lesions with smooth margins, homogeneous or relatively low signal at T1-weighted imaging and isointense signal at T2-weighted imaging compared with the liver, and uniform early contrast enhancement [59]. Larger adenomas may contain areas of necrosis, cystic degeneration, and hemorrhage. Chemical-shift images can identify the presence of intracellular lipid when signal dropout on opposed-phase T1-weighted gradient-recall echo sequences is present compared with the in-phase sequence. A signal dropout of more than 11.2% on the opposed-phase sequence allows 100% accuracy in distinguishing adenomas from metastatic adrenal tumors, although simple visual observation of a signal dropout is sufficient to diagnose most lipid-rich adenomas [63, 64]. There is essentially no difference in the ability of CT and MRI in diagnosing lipid-rich adrenal adenomas; however, CT is considered superior in diagnosing lipid-poor adenomas not detected by CSI MRI owing to its ability to assess for enhancement washout on CT [54, 63].

**Adrenocortical Carcinoma**

ACC (Fig. 9) accounts for approximately 40% of adrenal causes of CS and usually appears as a unilaterial large (mean size, 9 cm; range, 2–25 cm) heterogeneously enhancing soft-tissue mass, frequently with intratumoral necrosis or hemorrhage, with microscopic or coarse calcifications present in 30% of cases [28, 65]. ACC may contain small areas of intracytoplasmic lipid or macroscopic fat [65]. ACC may invade adjacent structures and show venous extension into the renal vein or inferior vena cava, as seen in 9–19% of cases [65]. Although ACC shows avid early enhancement, it does not show contrast washout on the 15-minute delayed phase to the same degree as an adenoma, allowing differentiation when the lesion is small and homogeneous and potentially mimicking an adenoma at imaging. ACC is bilateral in 2–10% of cases [65]. Metastatic disease is frequently found at presentation, commonly to the regional lymph nodes, lungs, liver, and bone [65]. At MRI, ACC usually has heterogeneous signal intensity due to areas of necrosis and hemorrhage. The T1-weighted imaging signal is typically isointense to hypointense to the liver, but there may be areas of high T1 signal due to hemorrhage. The T2-weighted imaging signal is typically hyperintense to the liver with heterogeneously increased signal in necrotic regions [65]. When small areas of intracytoplasmic lipid are present, CSI may show small nonuniform areas of signal decrease over less than 30% of the lesion area, in distinction to lipid-rich adenomas, which show uniform signal loss on CSI [65].
Primary Pigmented Nodular Adrenal Disease

The characteristic appearance of the adrenal glands in PPNAD is that they contain multiple small nodules (Fig. 10B), usually smaller than 6 mm, with atrophy of the intervening adrenal cortex due to the autonomous function of the nodules with resultant suppression of pituitary ACTH [29]. This can give rise to a knobby or irregular adrenal gland contour [29]. The adrenal glands may be normal in size or slightly enlarged. The adrenal glands may even appear normal at CT; therefore, when evaluating a case of established ACTH-independent CS, the normal appearance of the adrenal glands should prompt a search for supporting features of the Carney complex, such as cardiac myxomas, which can be asymptomatic but potentially fatal [9, 29]. These cases may further benefit from genetic testing for mutations of the PRKARIA gene to determine whether the Carney complex is present [9, 29]. At MRI, the adrenal nodules display low signal on T1- and T2-weighted images compared with the surrounding atrophic cortex [66]. Rarely, PPNAD may have macronodules larger than 1 cm [66].

Adrenocorticotropic Hormone–Independent Macronodular Adrenal Hyperplasia

In contrast to PPNAD, ACTH-independent macronodular adrenal hyperplasia has a pathognomonic appearance at imaging. Both adrenal glands are massively enlarged and typically have a nodular distorted contour (Fig. 11). Nodules typically range from 0.1 to 5.5 cm and appear hypodense at CT because of a lipid-rich matrix [67]. The enlarged adrenal glands frequently span from the diaphragm to the level of the renal hilum. At MRI, the adrenal nodules are hypointense relative to the liver on T1-weighted images and iso- to hyperintense relative to the liver on T2-weighted images [33, 67]. A signal dropout is noted on CSI because of the high lipid content.

Treatment of Cushing Syndrome

Surgery

Transsphenoideal endoscopic selective resection of the pituitary adenoma (selective adenomectomy) is the treatment of choice for Cushing disease because it offers a high potential for cure, with remission in 70–90% of cases [68, 69]. The tumor can be approached endoscopically via the nose or through a small opening in the upper gum just above the central incisors and then through the sphenoid sinus. If the adenoma cannot be detected visually, half or more of the gland can still be removed. After resection, patients receive steroid replacement therapy because cortisol levels are expected to decrease. Unilateral adrenalectomy is indicated for adrenal adenoma and ACC, and bilateral adrenalectomy is the recommended and curative treatment for PPNAD and ACTH-independent macronodular adrenal hyperplasia [32].

Bilateral adrenalectomy is the final therapeutic line in the treatment of refractory Cushing disease and can be performed in severely ill patients to immediately remove the source of high cortisol production. The resection of both adrenal glands causes permanent hypoadrenalism, and patients require lifelong glucocorticoid and mineralocorticoid replacement. Furthermore, approximately 50% of these patients risk developing Nelson syndrome, with enlargement of the pituitary adenoma, increases in serum ACTH levels, and hyperpigmentation of the skin resulting from increased melanocyte-stimulating hormone secretion [70]. Radiation therapy to the pituitary gland delays the onset of Nelson syndrome [71].

Complete surgical removal of the tumor producing ACTH is curative. When the patient is not a suitable candidate for operation, medical treatment to reduce cortisol levels may be used, but only for refractory cases. Adrenalectomy could be the final decision.

Radiation of the Pituitary Gland

When complete surgical excision of the pituitary adenoma is not possible (e.g., adenoma infiltrating the cavernous sinus or optic chiasm or encasing the internal carotid artery), or if the patient declines surgery, then radiation therapy to the pituitary gland offers the possibility of remission [70]. Radiation therapy may consist of photon or proton beam and may be fractionated or stereotactic depending on the size and location of the tumor. In most cases of radiation therapy, there is a significant delay between the time of treatment and the normalization of cortisol levels, necessitating medical management of hypercortisolemia during this period.

Medical Therapy

Pharmacotherapy for CS includes drugs that act on the adrenal gland to block cortisol synthesis (e.g., ketoconazole and metyrapone), reduce ACTH secretion in Cushing disease (e.g., octreotide and pasireotide), or block cortisol action by acting as a glucocorticoid receptor antagonist (e.g., mifepristone). These medications are not used as a definitive treatment but rather as a bridge to surgery or radiotherapy. Medical treatment of CS also aims to control symptoms of the disease, such as hypertension, hyperglycemia, and electrolyte disturbances. Gradual withdrawal of glucocorticoids in iatrogenic CS is mandatory because the body becomes accustomed to a high level of glucocorticoids.

Summary

The accurate diagnosis and characterization of CS requires a multimodality approach, including clinical assessment, biochemical analysis, and imaging studies. Cushing disease is the most common cause of ACTH-dependent CS, and contrast-enhanced pituitary MRI is the preferred study to detect pituitary adenomas, with bilateral inferior petrosal sinus sampling used in equivocal or discordant cases. In cases of ectopic ACTH production, CT, MRI, nuclear medicine scans, and selective vascular sampling could be used to localize the ectopic ACTH-producing tumor. In ACTH-independent CS, an adrenal protocol CT is the preferred initial study and can diagnose adrenal adenomas with very high accuracy and differentiate these from other adrenal abnormalities leading to CS. MRI, with CSI, is also highly accurate in the workup of cortisol-secreting adrenal abnormalities. Adrenal venous sampling can accurately localize the source of cortisol excess and may be especially helpful in diagnosing unilateral or bilateral excess cortisol secretion in patients with bilateral adrenal masses. In summary, a multifaceted diagnostic approach making use of the appropriate imaging modalities is required to accurately diagnose the cause of CS and to facilitate appropriate and timely clinical management.

References

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Imaging of Cushing Syndrome


Fig. 1—Clinical features of Cushing syndrome in various patients. A, 38-year-old woman with Cushing disease. Photograph shows central obesity. B, 28-year-old man with ectopic secretion of adrenocorticotropic hormone (ACTH) from thymic neuroendocrine tumor. Photograph of torso shows multiple thick red-purple strie on abdominal wall, chest, and upper arms. C, 12-year-old girl with Cushing syndrome secondary to ectopic ACTH secretion from thymic neuroendocrine tumor. Photograph of legs shows multiple wide purple striae. (Fig. 1 continues on next page)
Fig. 1 (continued)—Clinical features of Cushing syndrome in various patients.
D, 24-year-old woman with Cushing syndrome secondary to ACTH-secreting metastatic pituitary carcinoma. Sagittal CT reconstruction of lumbar spine shows multilevel vertebral endplate depressions with loss of vertebral body height from osteoporotic spine fractures.
E, 54-year-old man with Cushing disease. Coronal CT reconstruction of right hip shows subchondral lucency of femoral head, crescent sign, and surrounding sclerosis from avascular necrosis of femoral head.

Fig. 2—51-year-old man with Cushing disease. Coronal contrast-enhanced T1-weighted MR image of pituitary gland shows hypoenhancing microadenoma of right aspect of pituitary gland (arrow).

Fig. 3—56-year-old man with Cushing disease. Contrast-enhanced coronal T1-weighted image of sella shows peripherally enhancing macroadenoma (arrow) with nonenhancing central necrotic area and its relation to cavernous sinus and carotid arteries, with no evidence of invasion or encasement.

Fig. 4—55-year-old woman with adrenocorticotropic hormone (ACTH)–dependent Cushing syndrome and ectopic secretion of ACTH resulting from small cell lung cancer.
A, Axial contrast-enhanced chest CT shows spiculated left upper lobe pulmonary nodule (arrow) that was pathologically proven to be small cell carcinoma.
B, Bilateral diffuse enlargement and thickening of adrenal glands from ACTH–induced adrenocortical hyperplasia (arrows) is common finding in ACTH-dependent Cushing syndrome, as seen on axial CT image.
Imaging of Cushing Syndrome

Fig. 5—57-year-old woman with bronchial neuroendocrine tumor and ectopic adrenocorticotropic hormone (ACTH) syndrome. Axial SPECT/CT octreotide scan through upper chest localized ectopic source of ACTH to 2-cm bronchial neuroendocrine tumor (arrow) in right upper lobe.

Fig. 6—12-year-old girl with adrenocorticotropic hormone (ACTH)—dependent Cushing syndrome and ectopic secretion of ACTH from thymic neuroendocrine tumor.

A. Contrast-enhanced axial CT shows large partially calcified tumor (arrow) along anterior mediastinum that was pathologically proven to be thymic neuroendocrine tumor.

B. Anterior (left) and posterior (right) 24-hour planar images from octreotide scan show increased uptake (arrows) that corresponds to region of patient’s large mediastinal mass seen on CT and is consistent with somatostatin receptor–positive tumor. There is otherwise physiologic uptake in liver, spleen, kidneys, bladder, and colon.

C. Coronal reconstruction CT image shows diffuse bilateral adrenal enlargement of adrenal glands (arrows) representing ACTH-induced adrenocortical hyperplasia. Diffuse hepatic steatosis is noted, which is present at CT in 20% of patients with active Cushing syndrome [72]. Patient was ultimately treated with bilateral adrenalectomy.
Fig. 7—23-year-old man with adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome and ectopic ACTH secretion from pancreatic neuroendocrine tumor.
A. Contrast-enhanced axial CT of abdomen shows heterogeneous retroperitoneal soft-tissue masses (arrow) with bilateral diffuse enlargement of adrenal glands, representing ACTH-induced adrenal hyperplasia.
B. Coronal SPECT/CT image of octreotide scan shows intense uptake in pancreatic neuroendocrine tumor (arrow), representing ectopic source of ACTH.

Fig. 8—35-year-old woman with adrenal adenoma causing Cushing syndrome. Contrast-enhanced axial CT image shows small well-defined ovoid nodule (arrow) arising in left adrenal gland that proved to be hormonally active adrenal adenoma.

Fig. 9—32-year-old man with adrenocortical carcinoma resulting in Cushing syndrome.
A. Unenhanced axial T1-weighted MR image shows large heterogeneous right adrenal mass (arrow) with central areas of high T1 signal, representing intratumoral necrosis and hemorrhage.
B. Gross pathology photograph of resected adrenocortical carcinoma shows large tumor with areas of necrosis.
Imaging of Cushing Syndrome

Fig. 10—17-year-old girl with primary pigmented nodular adrenocortical disease and adrenocorticotropic hormone–independent Cushing syndrome.
A. Contrast-enhanced axial CT image of left adrenal gland shows normal-sized adrenal gland with several small subtle nodules measuring less than 5 mm (arrows).
B. Photo shows gross pathologic specimen of resected adrenal gland with multiple small yellow-brown adrenal nodules.

Fig. 11—43-year-old man with adrenocorticotropic hormone–independent macronodular adrenal hyperplasia and Cushing syndrome.
A. Contrast-enhanced axial CT image of abdomen shows fairly symmetric diffuse bilateral nodular enlargement of adrenal glands.
B. Photograph shows gross pathologic specimen of adrenal glands with multiple parenchymal nodules. R = right, L = left.
Fig. 12—Algorithm for diagnosis and management of Cushing syndrome. Chart was created using previously published data [6, 16, 34]. UFC = urinary free cortisol, ACTH = adrenocorticotropic hormone, IPSS = inferior petrosal sinus sampling.