Imaging of Adrenal-Related Endocrine Disorders

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KEYWORDS

• Endocrine disorders • Endocrine abnormality • Adrenal pathologies • Imaging • Excess hormone secretion

KEY POINTS

- Endocrine disorders associated with adrenal pathologies can be caused by insufficient adrenal gland function or excess hormone secretion.
- Excess hormone secretion may result from adrenal hyperplasia or hormone-secreting (ie, functioning) adrenal masses.
- Based on the hormone type, functioning adrenal masses can be classified as cortisol-producing tumors, aldosterone producing tumors, and androgen-producing tumors, which originate in the adrenal cortex, as well as catecholamine-producing pheochromocytomas, which originate in the medulla.
- Nonfunctioning lesions can cause adrenal gland enlargement without causing hormonal imbalance.
- Evaluation of adrenal-related endocrine disorders requires clinical and biochemical workup followed by imaging evaluation to reach a diagnosis and guide management.

INTRODUCTION

A wide spectrum of pathologies can affect the adrenal gland, including a range of functioning benign and malignant masses that secrete increased amounts of adrenal hormones as well as nonfunctioning tumors that do not affect hormone levels. Functioning tumors or hyperplasia of the adrenal cortex can cause Cushing syndrome (CS) from cortisol excess, Conn syndrome from aldosterone overproduction, or hyperandrogenism from androgen excess. Pheochromocytomas are tumors that arise from the adrenal medulla and secrete catecholamines. The other well-known adrenal pathology is adrenal insufficiency, which is characterized by low levels of adrenal hormones, and may result from adrenalectomy, autoimmune disorders, granulomatous diseases, hemorrhage, bilateral adrenal metastases, or infections causing adrenal gland destruction and hypofunction. The diagnosis of adrenal-related endocrine disorders is usually based on physical examination and biochemical workup, followed by imaging evaluation. Proper management of endocrine disorders, especially those that are neoplastic, requires a multidisciplinary team collaboration among endocrinologists, radiologists, pathologists, and surgeons. In this review, we focus on adrenal disorders associated with an endocrine abnormality and will not include nonfunctioning adrenal tumors.

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IMAGING EVALUATION

Imaging evaluation guides the appropriate management of adrenal-related endocrine disorders. Computed tomography (CT) with adrenal mass–dedicated protocol is the reference standard imaging modality for assessment of adrenal gland pathologies. An adrenal CT is performed with 2.5 to 3 mm thin slices, before and after intravenous administration of 100 to 150 mL of iodinated contrast material.[1] The adrenal mass protocol includes density measurement of the mass on noncontrast CT. An unenhanced attenuation value less than 10 Hounsfield units (HU) is characteristic of a lipid-rich adenoma. However, for adrenal masses with attenuation values greater than 10 HU, the absolute percentage of enhancement washout is calculated by measuring the unenhanced attenuation, the enhanced attenuation at 60 seconds, and attenuation 15 minutes after contrast injection to show rapid enhancement and rapid washout.

CT is often the first-line modality for adult adrenal imaging due to its wide availability, reproducibility, good temporal resolution and better spatial resolution than MR imaging.[2] Adrenal abnormalities can be detected and characterized using contrast-enhanced CT with or without noncontrast images, as mentioned previously.

Other imaging modalities, such as MR imaging and PET with fluorodeoxyglucose (FDG) or other specialized radioactive tracers such as gallium-68 DOTATATE are useful as adjuncts to CT when CT is negative or inconclusive.[3] Ultrasonography can be considered as an imaging modality for adrenal lesions in neonates and young children[4]; however, because the echogenicity of adrenal glands is close to the echogenicity of retroperitoneal fat, it is a challenge to visualize adrenal glands on ultrasound in older children and adults. In addition, ultrasound has limitations in identifying small lesions, and overlying bowel gas can be an impediment to adequate visualization.

MR imaging, which is discussed in greater detail later in this article, is often used as problem solver, especially when CT is contraindicated or inconclusive. MR imaging has a particular advantage of the lack of ionizing radiation. Chemical shift in-phase and opposed-phase are the most important MR imaging pulse sequences for characterizing adrenal masses by detecting intracytoplasmic lipid, high level of which is most often indicative of benign adrenal adenoma, with some exceptions such as lipid-containing metastases, collision tumors, or adrenocortical cancers. Ultimately, CT has been found to have the upper hand, compared with MR imaging, for differentiating between lipid-poor adrenal adenomas,[5] which show characteristic delayed postcontrast washout without detectability of lipid on chemical shift MR imaging, and other indeterminate adrenal masses. T2-weighted MR imaging may be helpful in the diagnosis of pheochromocytoma, which demonstrates marked hyperintensity; also known as “lightbulb sign.”[6]

Nuclear medicine imaging modalities such as MIBG and indium-111 octreotide and gallium-68 DOTATATE PET are commonly used to evaluate pheochromocytoma. FDG-PET shows promise in the differentiation of malignant cortical lesions from benign masses. Malignant lesions show increased FDG uptake, and FDG-PET has been shown to have 94% to 100% sensitivity and 80% to 100% specificity in the detection of malignant masses.[3]

OVERVIEW OF ADRENAL-RELATED ENDOCRINE DISORDERS

Endocrine disorders associated with adrenal pathologies may be subclinical or clinical and can be classified into hypofunctioning disorders, such as adrenal insufficiency, or hyperfunctioning disorders, such as hyperaldosteronism, hypercortisolism, catecholamine excess, and hyperandrogenism.

Adrenal Insufficiency

Primary adrenal insufficiency occurs due to partial or complete destruction of the adrenal cortex, and patients with this condition may present with hyponatremia, hyperkalemia, fatigue, muscle weakness, hypotension, weight loss, abdominal pain, and hyperpigmentation. Common etiologies of primary adrenal insufficiency are autoimmune disease (ie, Addison disease), granulomatous diseases such as tuberculosis, other infections, neoplasms such as metastases and lymphoma, adrenal gland hemorrhage, adrenoleukodystrophy, and congenital adrenal hyperplasia.[7–9]

Screening tests for adrenal insufficiency include morning cortisol and adrenocorticotropic hormone (ACTH) levels or a high-dose cosyntropin (synthetic ACTH) stimulation test. Cortisol levels that fail to rise after ACTH stimulation and remain lower than 20 μg/dL indicate adrenal insufficiency.[10,11] In primary adrenal insufficiency, the synthesis and release of adrenocortical hormones are impaired.[11] The next step after the diagnosis of primary adrenal insufficiency is to check adrenal autoantibodies for autoimmune adrenal insufficiency. If autoantibodies are negative, very long chain fatty acids can be tested for adrenoleukodystrophy, serum 17-hydroxyprogesterone level

can be measured for congenital adrenal hyperplasia, and CT can be performed to detect adrenal hemorrhage, infection, infiltration, or malignancy.[11] In adrenoleukodystrophy, very long chain fatty acids are accumulated in tissue and body fluids, and the clinical manifestations can be seen as central nervous system demyelination and primary adrenal insufficiency. Adrenal insufficiency is usually associated with cerebral adrenoleukodystrophy or adrenomyeloneuropathy involving the spinal cord and peripheral nerves, but in 8% of cases adrenal insufficiency is the only clinical manifestation.[12] Loes and colleagues[13] described 5 different MR imaging patterns of cerebral adrenoleukodystrophy, and the radiologic finding indicative of adrenal involvement is adrenal cortex atrophy.[12] In congenital adrenal hyperplasia, bilateral enlarged adrenal glands, wrinkled surface, and cerebriform pattern are characteristic ultrasound findings; however, the adrenal glands may also appear normal.[14] Therefore, ultrasonography should only be used as an adjunct to CT or MR imaging when adrenal hyperplasia is suspected.

CT imaging findings of primary adrenal insufficiency depend on the etiology and course of the disease. For instance, adrenal hemorrhage can present as a high-attenuation mass in the acute stage, then decrease in attenuation with aging of the hematoma.[15]

Infectious diseases and autoimmune and granulomatous disorders can cause bilateral enlargement of the glands[16] in the acute/subacute stage, with atrophy and often calcification of adrenal glands in the chronic stage. For example, Addison disease is considered subacute when present for less than 2 years, and in these cases, CT usually shows bilateral enlarged adrenal glands with occasional central necrosis and peripheral rim enhancement due to adrenalitis.[17,18]

In the chronic stage of adrenal insufficiency, CT shows bilateral adrenal gland atrophy. Calcifications are seen in 50% of cases of primary adrenal insufficiency secondary to tuberculosis; however, calcifications due to tuberculosis cannot be distinguished radiologically from other causes of calcifications, such as prior hemorrhage or idiopathic calcifications. Clinical and hormonal correlation is the key in such cases.[19–21]

Adrenal hemorrhage can result from blunt trauma, anticoagulation therapy, sepsis, or stress following surgery or severe burns, or it can be a complication of adrenal venous sampling.[22] In the setting of trauma, adrenal hemorrhage usually occurs in trauma of higher severity, and isolated adrenal hemorrhage is rare. Hemorrhage can also be seen in both benign and malignant masses such as adenomas, adrenal cortical carcinomas, myelolipomas, and pheochromocytomas.[23] Bilateral involvement can be seen in 20% of adrenal hemorrhage cases.[22] The most common imaging feature of hemorrhage, a high-attenuating adrenal mass, is seen in 83% of cases on unenhanced CT (**Fig. 1**). On MR imaging, adrenal hemorrhage shows intermediate signal intensity on T1-weighted images and low signal intensity on T2-weighted images in the acute stage and high signal intensity on both T1-weighted and T2-weighted images in the subacute stage. The typical appearance of chronic adrenal hemorrhage includes high signal intensity on T1-weighted images and hypointense peripheral rim on T2-weighted images. The high signal intensity on T1-weighted images can be due to methemoglobin, and hypointense peripheral rim on T2-weighted images is seen due to hemosiderin. Hematomas gradually decrease in size and may completely resolve or develop calcifications within a few months.[24]

Granulomatous infections such as tuberculosis or histoplasmosis account for 10% to 30% of primary adrenal insufficiency cases.[21] CT findings in the acute stage are bilateral adrenal enlargement, central necrosis, and peripheral rim enhancement. In the subacute and chronic stages, the adrenal glands become atrophic and calcified.

Other causes of adrenal insufficiency include lymphoma (**Fig. 2**) and metastases (**Fig. 3**). Lymphomatous adrenal lesions are usually homogeneous and large, but they can also be heterogeneous due to necrosis or hemorrhage. Adrenal lymphoma is bilateral in 50% of cases and is usually accompanied by retroperitoneal lymphadenopathy.[25] On CT, adrenal lymphoma usually demonstrates soft tissue attenuation and shows mild progressive enhancement.[26] On MR imaging, adrenal lymphoma typically exhibits low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with mild to moderate enhancement.[27]

The adrenal glands are a common site for hematogenous metastases because of their abundant blood supply, and most patients with adrenal metastases have a history of cancer. In a study by Song and colleagues,[28] not a single malignant lesion was found in 1049 patients without a history of malignancy who had adrenal nodules incidentally discovered at imaging. It is also rare to find an incidental adrenal metastasis at the initial presentation of an unknown primary malignancy. In a series of 1639 patients with unknown primary malignancy, the adrenal glands were involved in only 6%, and involvement was limited to the adrenal glands in only 0.2%; furthermore, all of the

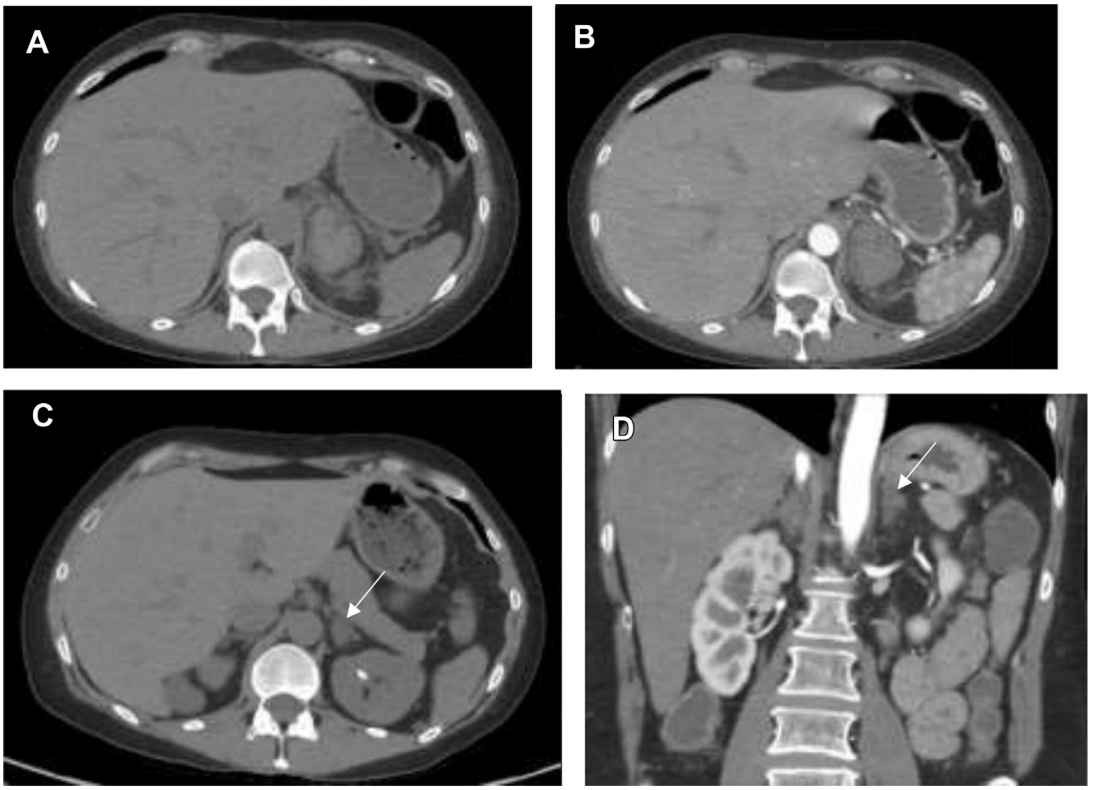

Fig. 1. A 51-year-old patient presented to the emergency department with abdominal pain. Axial unenhanced CT (*A*) and axial image of contrast-enhanced CT (*B*) demonstrate a well-circumscribed, rounded 3.2 × 4.2 cm mass involving the left adrenal gland with attenuation of 51 HU and no significant postcontrast enhancement, suggestive of hematoma. In the following 3 months, the patient had adrenal insufficiency symptoms in the form of fatigue, abdominal pain, and weakness. The workup for adrenal bleeding showed a heterozygous factor V Leiden mutation. Axial unenhanced CT (*C*) and coronal reformatted images of contrast-enhanced CT (*D*) performed 3 months later for follow-up showed interval resolution of the hematoma with diffuse left adrenal gland thickening (*arrow*).

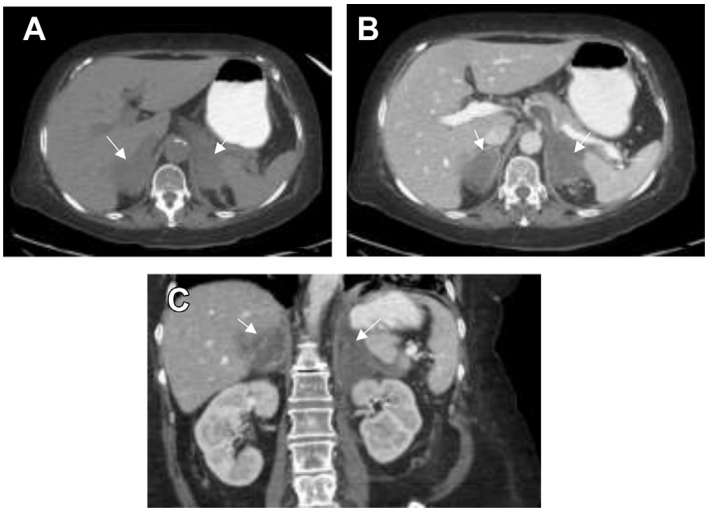

Fig. 2. A 70-year-old patient with a history of Burkitt lymphoma presented with adrenal insufficiency due to lymphomatous involvement of the bilateral adrenal glands. Axial unenhanced CT (*A*), and axial (*B*) and coronal (*C*) enhanced CT demonstrate bilateral enhancing adrenal masses (*arrows*).

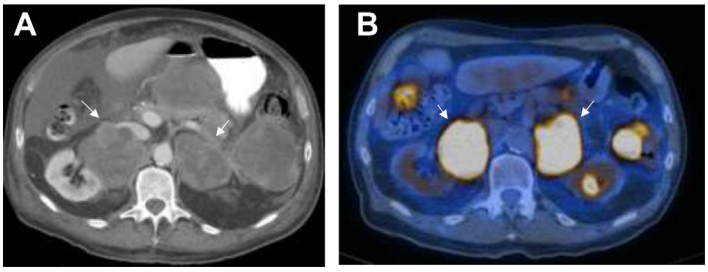

Fig. 3. A 76-year-old patient with adenocarcinoma of the lung with metastases to the bilateral adrenal glands, kidneys, bones, and mesentery presented with adrenal insufficiency. Axial enhanced CT (*A*) demonstrates bilateral adrenal masses (*arrows*), with the right adrenal mass indenting the right kidney collecting system. PET/CT (*B*) demonstrates increased FDG uptake in the bilateral adrenal glands (*arrows*). Biopsy of the right adrenal gland showed metastatic non–small cell carcinoma.

adrenal lesions were 6 cm or larger, and 75% of the patients had bilateral involvement.[29] Metastases to the adrenal glands most commonly originate from lung, breast, liver, kidney, and gastric cancers.[24] On CT, adrenal metastases usually have attenuation values greater than 10 HU on unenhanced series, and they show irregular peripheral or heterogeneous enhancement on contrast-enhanced series. Unlike adenomas, metastases enhance rapidly but do not exhibit enhancement washout, with the exception of some hypervascular metastatic lesions from primary tumors such as renal cell carcinoma and hepatocellular carcinoma, which can show rapid washout and hence can be misdiagnosed as adenomas.[30] Similarly, the presence of intracellular fat is highly specific for benign adenoma; however, some metastases, such as those from renal cell or hepatocellular carcinoma, can rarely contain intracellular lipid and mimic adrenal adenomas.[31–33] Associated hemorrhage and calcifications have been also described within these lesions. On MR imaging, metastatic masses typically demonstrate high signal intensity on T2-weighted images and low signal intensity on T1-weighted images and with heterogeneous postcontrast enhancement.

Hyperaldosteronism

Hyperaldosteronism can be primary, also known as Conn syndrome (the classic description of which is that of an aldosterone-producing adenoma), or secondary depending on the renin level. Whereas aldosterone levels in both primary and secondary hyperaldosteronism are high, the renin level is low in primary and high in secondary hyperaldosteronism (such as seen with a renin-secreting tumor or renovascular hypertension). Hyperaldosteronism presents with hypertension (typically refractory to multidrug therapy), hypokalemia (which is not always present), metabolic alkalosis, muscle cramps/weakness, headache, increased thirst, and frequent urination.

Common etiologies of secondary hyperaldosteronism are congestive heart failure, cirrhosis, nephrotic syndrome, renal artery stenosis, renin-secreting tumors, or diuretic use. Adrenal lesions in primary hyperaldosteronism can be unilateral or bilateral adrenal adenoma(s) (**Fig. 4**), adrenal hyperplasia, or adrenal carcinoma. Conn syndrome is caused by an aldosterone-producing adenoma in 35% of cases and bilateral idiopathic hyperplasia in 60% of cases.[34,35]

Screening tests for hyperaldosteronism include measuring the plasma renin activity (PRA) and plasma aldosterone concentration (PAC). Primary aldosteronism is suggested if the PAC:PRA ratio is greater than 20, and PAC levels greater than 20 ng/dL and PRA less than1 ng/mL per hour in the setting of spontaneous hypokalemia confirm the diagnosis. If both PRA and PAC are elevated, etiologies for secondary hyperaldosteronism should be further investigated. On the other hand, decreased PRA and PAC levels should prompt an investigation of other etiologies such as exogenous mineralocorticoids (eg, licorice ingestion) and CS.[36]

For confirmation of primary aldosteronism, measuring 24-hour aldosterone levels after oral sodium loading, measuring aldosterone response to intravenous saline infusion, and fludrocortisone suppression and captopril challenge tests may be used.[37] Aldosterone level higher than 10 ng/dL in a saline infusion test and direct renin concentration lower than 24 mIU/mL and PRA lower than 2 ng/mL hour in fludrocortisone suppression test are confirmatory results.[36]

After the biochemical confirmation of primary hyperaldosteronism, adrenal imaging should be pursued. If the patient has a unilateral adrenal adenoma on imaging and is younger than 40 years, unilateral adrenalectomy is the recommended treatment because the likelihood of this representing an incidental nonfunctional adrenal adenoma is only 1% to 2%.[38] Patients older than 40 years with a unilateral adrenal adenoma and patients with

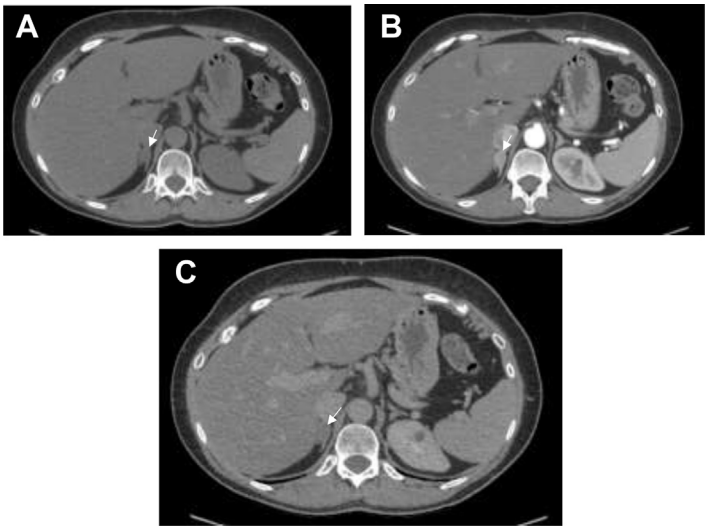

Fig. 4. A 53-year-old woman with a 14-year history of hypertension requiring multiple medications and hypokalemia with occasional muscle weakness and fatigue was referred to the endocrinology clinic while being treated for her breast cancer. Primary hyperaldosteronism was suspected. Axial unenhanced CT (*A*) demonstrates a well-circumscribed 1.5-cm oval mass involving the right adrenal gland with an attenuation of 19 HU. Contrast-enhanced CT in the portovenous phase (*B*) shows contrast uptake of the lesion, with attenuation of 106 HU. Delayed 15-minute axial CT (*C*) shows contrast washout with attenuation of 42 HU, yielding an absolute enhancement washout of 74%, characteristic of a lipid-poor adenoma (*arrow*).

normal glands or equivocal findings should be further investigated with selective adrenal venous sampling, which is the reference standard test for differentiating unilateral from bilateral adrenal disease.[39] A coincidental nonfunctioning neoplasm should be considered if adenomas are larger than 2 cm, because aldosteronomas are usually smaller than 1.5 cm.[40] If imaging shows bilateral adrenal gland thickening or micronodular changes, the diagnosis is bilateral adrenal hyperplasia or idiopathic hyperaldosteronism. If adrenal venous sampling confirms bilateral aldosterone production, medical management with an aldosterone receptor antagonist should be undertaken.[36] In addition, glucocorticoid-remediable aldosteronism, wherein aldosterone secretion is under the control of ACTH, also presents with nonlocalizing venous sampling test results.[41]

In this setting, adenomas can be detected on CT in only 70% of hyperaldosteronism cases. Aldosteronomas are typically homogeneous hypoattenuating nodules with attenuation less than 10 HU (if lipid-rich) and homogeneous contrast enhancement on CT, and they rarely show calcifications. Because the average diameter of aldosteronomas is less than 2 cm (approximately 20% measure <1 cm),[42] CT should be performed with a slice thickness of 5 mm or less. On MR imaging, they are iso- or hypointense relative to the liver on T1-weighted images and slightly hyperintense on T2-weighted images, with decrease in signal intensity on opposed-phase compared with in-phase pulse sequences.[42] It has been reported that aldosteronomas have the lowest attenuation values among hyperfunctioning adrenal adenomas.[42,43] As many as 50% of surgically proven aldosteronomas may be misdiagnosed as hyperplasia on CT.[44] Adrenal cortical hyperplasia is among the etiologies of patients presenting with excessive secretion of adrenal cortex hormones such as cortisol, aldosterone, and androgens, and 60% of hyperaldosteronism cases result from adrenal cortical hyperplasia. Adrenal cortical hyperplasia typically presents as smooth to slightly lobular, uniform enlargement, although macronodular morphology can be also seen. In diffuse hyperplasia, there is homogeneous enlargement of the entire gland, and the normal inverted V or Y configuration is maintained. The limbs of the adrenal glands usually measure more than 5 cm in length and more than 1 cm in thickness. The attenuation and signal intensity of cortical adrenal hyperplasia are usually similar to that of the normal gland (**Fig. 5**). In a small percentage of patients, low CT attenuation and signal drop on opposed-phased MR imaging can be seen, especially in cases with macronodules.[24,45,46]

Hypercortisolism

The chronic excess of cortisol causes CS, which presents with features that include obesity, moon facies, proximal muscle weakness, thin skin with easy bruising, violaceous striae, abnormal body fat distribution (ie, truncal obesity, fullness of the dorsal and supraclavicular fat pads), acne, hirsutism, hypertension, edema, low bone mass and fractures, amenorrhea, and impaired glucose tolerance. CS arises from exogenous glucocorticoid administration or endogenous overproduction of cortisol, which is either mediated by ACTH (ACTH-dependent CS) or caused by the neoplastic hypersecretion of cortisol from the

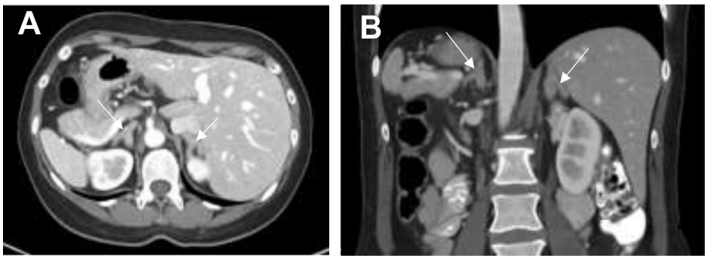

Fig. 5. A 43-year-old woman with situs inversus totalis and a history of Cushing disease due to a pituitary macroadenoma resected 7 years previously was referred to the endocrinology clinic for recurrent signs and symptoms of hypercortisolism. Axial contrast-enhanced CT (*A*) and coronal reformatted images of contrast-enhanced CT (*B*) show bilateral diffuse thickening of the adrenal glands (*arrows*), consistent with bilateral ACTH-driven adrenal hyperplasia.

adrenal cortex (ACTH-independent CS). ACTH-dependent hypercortisolism accounts for 80% of cases and is typically caused by an ACTH-producing pituitary tumor (Cushing disease) or more rarely by an ectopic ACTH-producing neuroendocrine tumor (NET) or a corticotropin-releasing hormone (CRH) producing tumor. The most likely source of ectopic ACTH production is a thoracic tumor (eg, bronchopulmonary NET, small cell lung cancer, thymic NET), but ectopic ACTH secretion can also occur in pancreatic NETs and, more rarely, pheochromocytomas and medullary thyroid carcinomas. CRH-producing tumors account for fewer than 1% of the cases.[5] ACTH-dependent CS can present with bilateral diffuse and uniform adrenal enlargement (see **Fig. 5**), which in time becomes nodular in appearance, and this is known as multinodular hyperplasia. Occasionally these ACTH-dependent macronodules grow larger and become autonomous, an entity called massive macronodular hyperplasia.[16,47] ACTH-independent CS can result from an adrenal adenoma, carcinoma, primary pigmented nodular adrenocortical disease (PPNAD) or ACTH-independent macronodular adrenocortical hyperplasia (**Fig. 6**), also known as bilateral macronodular adrenal hyperplasia. Adenomas account for 60% of adrenal-related CS cases, and the remaining 40% adrenal-related CS cases are caused by adrenocortical carcinoma.[5]

A clinical suspicion of CS should be followed by screening tests, which include a 24-hour urinary free cortisol, serum cortisol level after 1 mg dexamethasone administration at 11 PM the prior evening, and/or a late-night salivary cortisol level. If cortisol levels are not elevated but the clinical suspicion is high, repeat screening tests intermittently should be considered because CS can be cyclic in nature. ACTH levels should be evaluated after a diagnosis of CS is made. Whereas normal or overly elevated ACTH levels are consistent with ACTH-dependent disease, low normal or overtly low

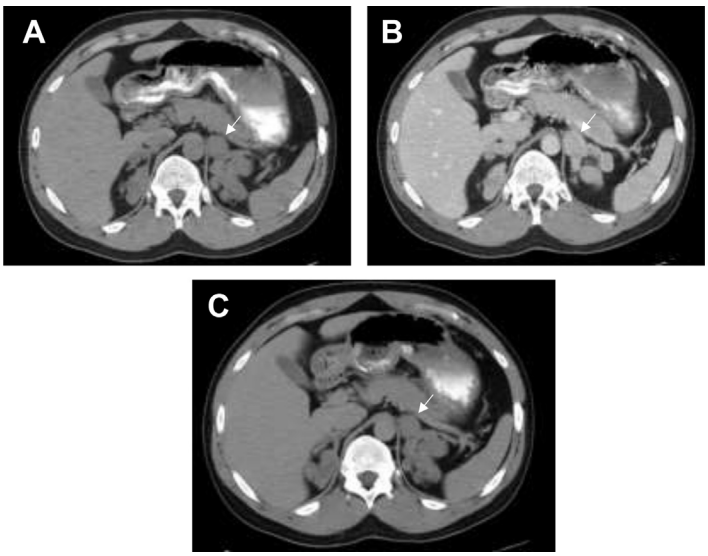

Fig. 6. A 33-year-old man with a 1-month history of hypertension and 20-pound weight gain, mostly abdominal, over the past 2 years and bilateral adrenal nodules was referred to the endocrinology clinic. He had an elevated 24-hour urinary free cortisol level, not suppressed by dexamethasone, and low ACTH concentration. ACTH-independent macronodular adrenal hyperplasia was suspected. Axial unenhanced CT (*A*) demonstrates bilateral well-circumscribed oval masses in the adrenal glands, the largest one measuring 2.7 cm in the left adrenal gland (*arrow*) with an attenuation of 38 HU. Contrast-enhanced CT in the portovenous phase (*B*) shows contrast uptake of the lesion with attenuation of 110 HU, and delayed 15-minute axial CT (*C*) shows contrast washout with attenuation of 59 HU, yielding an absolute enhancement washout of 71%, characteristic of a lipid-poor adenoma (*arrow*).

ACTH levels should prompt further evaluation of the adrenals. Pituitary MR imaging with and without contrast is performed once ACTH-dependent disease is identified. If MR imaging is negative for a pituitary cause or only a small pituitary lesion is detected, bilateral inferior petrosal sinus sampling can be considered. If inferior petrosal sinus sampling documents a peripheral source of ACTH secretion, additional imaging should be performed to evaluate for an ectopic ACTH-producing tumor.[5,48–51]

In the case of ACTH-independent CS, either CT or MR imaging should be performed to assess for an adrenal neoplasm. If adrenal imaging shows normal adrenal glands or micronodules, the Liddle test can be considered because patients with PPNAD show a paradoxic increase in cortisol secretion after the administration of dexamethasone.[52,53] In addition, adrenal venous sampling can be considered to determine laterality in selected cases.[54]

Adrenal adenomas are well-circumscribed round or ovoid lesions with homogeneous or slightly heterogeneous enhancement, measuring 1 to 5 cm.[55] A cortisol-secreting adenoma should be suspected when there is a focal mass in one adrenal gland and the other adrenal is smaller than normal, but there are no other reliable imaging findings that can discriminate the functionality of an adrenal adenoma. Low attenuation of adenomas due to their intracellular lipid content are diagnosed by unenhanced CT using a threshold of 10 HU, with high specificity of 98%. However, 30% of adenomas are lipid-poor and measure 10 HU or more on unenhanced CT.[56] Chemical shift imaging has been found to be sensitive in the differentiation of adenomas and other lesions with attenuation between 10 and 30 HU[57]; however, it has also been shown that chemical shift imaging is less sensitive than dynamic CT in lesions with attenuation less than 20 HU.[58] Diffusion-weighted imaging also has not been successful in the diagnosis of adenomas because of the overlap in apparent diffusion coefficient values among different adrenal masses.[59] Adenomas usually show fast and avid enhancement on early imaging (65–70 seconds) and fast washout. An absolute enhancement washout of more than 60% (100% × [attenuation in portal venous phase − attenuation in delayed phase]/[attenuation in portal venous phase − unenhanced attenuation]) or a relative enhancement washout of 40% (100% × [attenuation in portal venous phase – attenuation in delayed phase]/attenuation in portal venous phase) is highly sensitive and specific for the diagnosis of adrenal adenomas (**Fig. 7**).[56,60–62] On MR imaging, adrenal adenomas are homogeneous rounded lesions with low T1-weighted imaging signal, and they are isointense on T2-weighted imaging, with uniform early enhancement. A signal intensity index greater than 16.5%, which is calculated as 100 × ([in-phase signal intensity – opposed-phase signal intensity]/in-phase signal intensity), is highly specific for adrenal adenomas that contain intracellular lipid.[63]

Adrenocortical carcinoma is a rare tumor that can present as a palpable abdominal mass or abdominal/back pain. Approximately 40% of patients present with hormonal manifestations such as CS; virilization or feminization secondary to androgen or estrogen excess, respectively; or Conn syndrome.[64] Adrenocortical carcinoma usually presents as a large (>6 cm) heterogeneous mass due to hemorrhage and central necrosis.[65,66] It can invade adjacent structures and show venous extension. Adrenocortical carcinoma can be bilateral in rare cases and usually metastasizes to regional lymph nodes, lungs, liver, and bones.[67] Vascular invasion and distant metastases are found frequently at initial diagnosis. Adrenocortical carcinomas have precontrast attenuation values greater than 10 HU because of their lack of intracellular fat, and they enhance heterogeneously like other neoplastic adrenal lesions. Adrenocortical carcinomas have lower relative and absolute washout rates compared with adenomas.[45,68] Even though adrenocortical carcinomas show early rapid enhancement like adrenal adenomas, they do not show fast contrast washout. Calcifications can be found in 30% of adrenocortical carcinomas, and very rarely these tumors can have intracytoplasmic lipid (**Fig. 8**).[69] Only a few published cases have reported adrenocortical carcinoma with macroscopic fat.[70–72] An American College of Radiology (ACR) White Paper recommends follow-up CT or MR imaging in 12 months for benign-appearing, indeterminate adrenal nodules that are smaller than 4 cm.[73] In addition, according to the ACR White Paper, an increase of more than 20% (or an absolute increase of 5 mm) in the diameter is a suspicious feature on follow-up. It is also acknowledged that surgical series have shown a 4-cm cutoff to be sensitive for malignant lesions; however, more clinical evidence is needed to confirm this cutoff size.[74,75]

Another rare cause of CS is PPNAD, which is mostly associated with the Carney complex. PPNAD appears grossly as multiple small (<6 mm) pigmented nodules with atrophy of the involved adrenal cortex.[76] Other accompanying findings of Carney complex are soft tissue myxomas, especially affecting the atria; spotty skin pigmentation; and Sertoli cell tumors of the

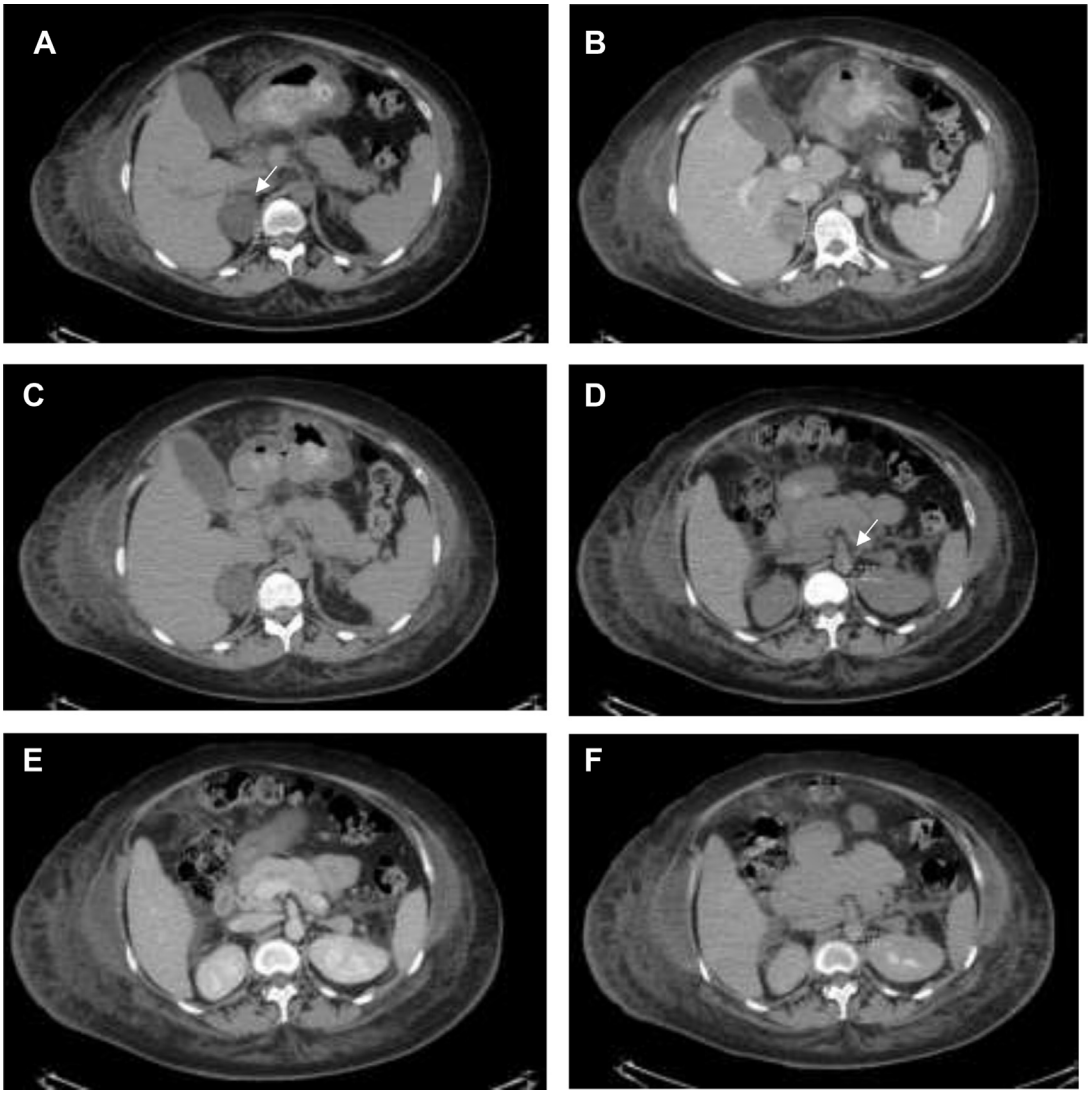

Fig. 7. A 28-year-old woman presented to the endocrinology clinic with recently diagnosed hypertension and elevated levels of testosterone during the second trimester of her pregnancy. An MR imaging from another center showed bilateral adrenal masses. Axial unenhanced CT after delivery (*A*) demonstrates a well-circumscribed oval mass measuring 4 cm involving the right adrenal gland (*arrow*) with an attenuation of 5 HU. Contrast-enhanced CT in the portovenous phase (*B*) shows contrast uptake of the lesion with attenuation of 56 HU. Delayed 15-minute axial CT (*C*) shows contrast washout with attenuation of 24 HU, yielding an absolute enhancement washout of 63%, characteristic of an adenoma. Axial unenhanced CT (*D*) demonstrates a well-circumscribed oval mass measuring 1.8 cm (*arrow*) involving the left adrenal gland with an attenuation of 15 HU. Contrast-enhanced CT in the portovenous phase (*E*) shows contrast uptake of the lesion with attenuation of 91 HU. Delayed 15-minute axial CT (*F*) shows contrast washout with attenuation of 40 HU, yielding an absolute enhancement washout of 67%, characteristic of a lipid-poor adenoma.

testes.[77] As previously mentioned, another cause of adrenal-related CS is ACTH-independent macronodular adrenal hyperplasia, which presents as bilateral enlarged adrenal glands with nodular contours on CT and hypodense lipid-containing nodules, ranging from 0.1 to 5.5 cm. On MR imaging, the nodules are hypointense relative to the liver on T1-weighted images and isointense to hyperintense on T2-weighted images with signal drop on opposed-phase images due to lipid content.[78]

Catecholamine Excess

Catecholamine excess (overproduction of epinephrine/norepinephrine and their metabolites,

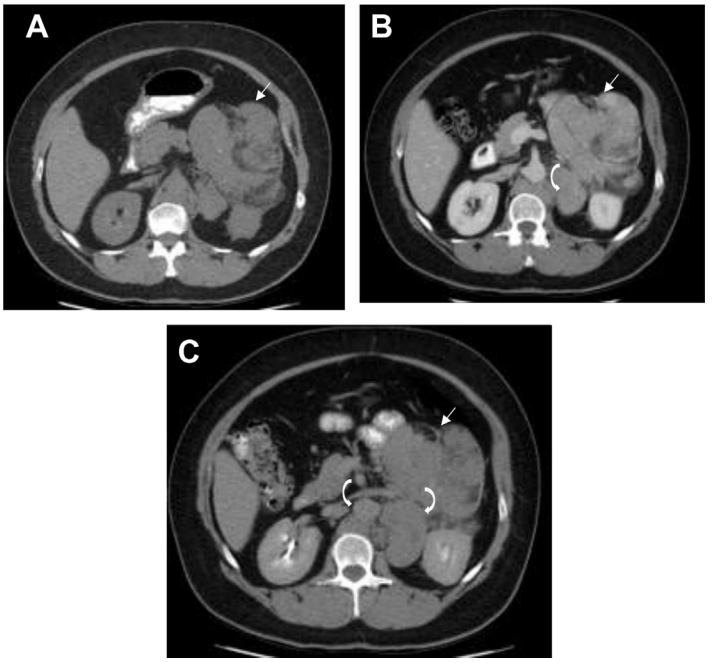

Fig. 8. A 42-year-old patient presented with an adrenal mass discovered at an outside facility. CT was performed for diagnostic workup of hypertension, diabetes mellitus, and hirsutism with elevated androgen and cortisol levels. Axial unenhanced CT (*A*), contrast-enhanced CT in the portovenous phase (*B*) and delayed 15-minute axial CT (*C*) demonstrate a large heterogeneous solid mass involving the left adrenal gland, measuring 13 cm in maximal dimension (*straight arrow* in *A*, *B* and *C*) with low attenuation areas, and speckles of calcifications with associated retroperitoneal lymphadenopathy (*curved arrows*). This mass was surgically resected and found to represent adrenocortical carcinoma.

metanephrine/normetanephrine) arises from secretory tumors of the adrenal medulla, including neuroblastoma and pheochromocytoma. Classic symptoms of catecholamine excess include hypertension, palpitations, headache, and sweating.

Pheochromocytomas are highly associated with hereditary disease, including multiple endocrine neoplasia types 2A and 2B (MEN2A and MEN2B), neurofibromatosis type 1, von Hippel-Lindau disease, and the group of familial paraganglioma syndromes due to mutations in the *SDHx* genes.[79] The historic "rule of 10 s," which suggested that 10% of pheochromocytomas are malignant, familial, extra-adrenal, diagnosed in children, or bilateral,[80] no longer holds true.[79] Pheochromocytomas can be multifocal and/or coexist with paragangliomas in 30% to 70% of cases, more so in familial cases or cases with a hereditary syndrome.[81] Pheochromocytomas are bilateral in 20% to 40% of cases, and up to 80% of those occurring in the pediatric population are associated with genetic mutation syndromes.[82] The incidence of pheochromocytoma in the hypertensive population is 0.1% to 0.6%, and the incidence in the general population is 0.05%, according to an autopsy series.[82]

In a patient clinically suspected to harbor a pheochromocytoma, free plasma metanephrines or 24-hour urinary metanephrines should be checked. If the metanephrine level is less than 2 times the normal level in a symptomatic patient, pheochromocytoma is highly unlikely. When the metanephrine level is 2 to 4 times higher than the normal level, repeat testing and an assessment of plasma or urine catecholamines should be pursued. When the metanephrine level is 4 times higher than the normal level, a pheochromocytoma can be diagnosed biochemically, and the next step should be imaging studies. If abdominal CT or MR imaging is negative, CT of the neck, chest, and pelvis should be considered to look for sympathetic paragangliomas.[83–87] If a mass is detected on anatomic imaging and there is no concern for multifocal disease, surgery can be performed after appropriate medical blockade. Genetic counseling and testing also should be pursued in all cases. If localizing studies are negative or there is a concern for multifocal disease (especially in cases of hereditary disease), functional imaging with 123I/131I MIBG or gallium-68 DOTATATE or 18F-FDG-PET/CT should be performed. Pheochromocytomas express somatostatin receptors and can be visualized with gallium-68 DOTA-coupled peptides such as DOTATATE. Chang and colleagues[3] showed that gallium-68 DOTATATE PET/CT detected a similar number of lesions with significantly greater lesion-to-background contrast compared with F-18 FDG-PET/CT.

Pheochromocytomas are usually homogeneous; however, they can present as heterogeneous

lesions due to intratumoral hemorrhage and necrosis as they get larger, and they can also be cystic. Calcification is an accompanying finding in 10% of cases, and the presence of intracytoplasmic fat can exclude pheochromocytoma.[6] Most pheochromocytomas show intense enhancement in the 70-s phase of contrast enhancement, and they tend to enhance more in the portal venous phase than in the arterial phase. They have washout characteristics similar to malignant lesions with prolonged enhancement (**Fig. 9**); however, approximately one-third of pheochromocytomas show washout values similar to adenomas.[6,83,88] On CT, pheochromocytomas usually have attenuation values higher than those of adenomas and similar to those of muscles. On MR imaging, they have high signal intensity on T2-weighted images, classically described as "light bulb bright"[89]; however, approximately 30% of pheochromocytomas can show intermediate to low signal intensity on T2-weighted images due to cystic degeneration or hemorrhage.[56]

Similar to adrenocortical carcinomas, reliable imaging findings to differentiate malignant from benign pheochromocytomas are distant metastases or local invasion into adjacent organs and vasculature.[90]

Although evaluating imaging studies for pheochromocytoma, special attention should be paid to the findings of potential accompanying syndromes. For instance, the MEN2 syndromes can present with thyroid tumors and parathyroid lesions (MEN2A) or megacolon (MEN2B). Radiologically detectable lesions in von Hippel-Lindau disease include central nervous system hemangioblastomas, renal cysts, renal cell carcinomas, and pancreatic cysts, cystadenomas, and NETs. In patients with neurofibromatosis, neurofibromas, optic nerve gliomas, or other central nervous system lesions or lung lesions can be seen. Tuberous sclerosis can present with subependymal tubers, renal angiomyolipomas, renal cysts, renal cell carcinomas, cardiac rhabdomyomas, and pulmonary lymphangiomatosis. In the familial paraganglioma syndromes, gastrointestinal stromal tumor and renal cell carcinoma can occur. Finally, the Carney complex is associated with extra-adrenal paraganglioma, gastrointestinal stromal tumor and pulmonary chondroma.[91–93]

Hyperandrogenism

The most common etiology of hyperandrogenism is polycystic ovary syndrome (PCOS). Other causes include late-onset 21-hydroxylase deficiency and other steroidogenic enzyme deficiencies; ovarian disorders such as stromal luteoma, ovarian hyperthecosis, and Sertoli-Leydig cell tumor[94]; and adrenocortical tumors. Other endocrine diseases such as ACTH-dependent CS and acromegaly can also cause hyperandrogenism. Common exogenous causes of hyperandrogenism are drugs with androgenic effects, such as testosterone and anabolic steroids.[95] Hyperandrogenism is a difficult diagnosis in men, whereas it can be easier in women who present with acne, increased body/facial hair, deepening of the voice, clitoral enlargement, and menstrual abnormalities.

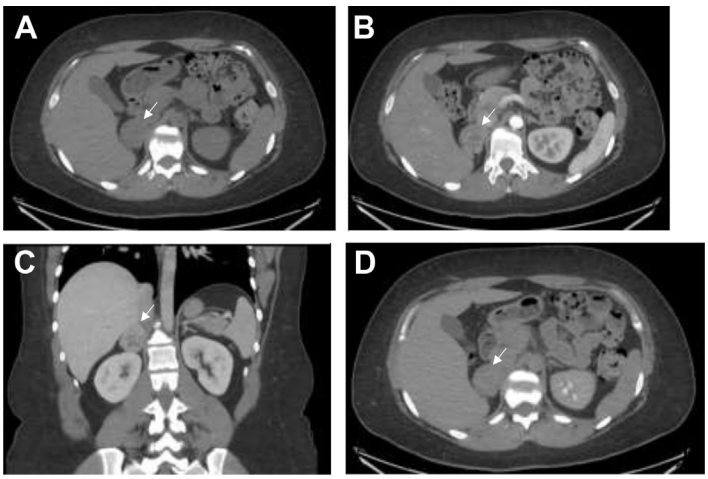

Fig. 9. A 34-year-old woman presented to the endocrinology clinic with an incidental adrenal mass discovered on CT at an outside facility performed after a motor vehicle accident. She reported a history of hypertension and worsening anxiety over the past year. Axial unenhanced CT (*A*) demonstrates a well circumscribed oval mass measuring 4.2 cm in maximal dimension involving the right adrenal gland with a precontrast attenuation of 28 HU. Contrast enhanced CT in arterial phase (*B*) shows a heterogeneously enhancing mass with attenuation of 56 HU, in the context of increased plasma metanephrines, compatible with pheochromocytoma (*arrow*). Coronal reformatted image of CT in the venous phase (*C*) demonstrates attenuation of 91 HU in the mass. Delayed 15-minute axial CT (*D*) shows contrast washout with attenuation of 58 HU, yielding an absolute enhancement washout of 52%. This mass was surgically resected and pathologically proven to represent pheochromocytoma (*arrows* in *A-D*).

To screen for hyperandrogenism, the levels of total testosterone, follicle-stimulating hormone, luteinizing hormone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and 17-hydroxyprogesterone (17OHP) should be measured. In women, if the total testosterone level is greater than 200 ng/dL and DHEAS is greater than 500 ug/dL, imaging should be done to assess for an adrenal cause; however, if DHEAS is normal or minimally elevated, ovarian causes such as ovarian androgen-secreting tumors or hyperthecosis should be further investigated with pelvic ultrasonography, CT, or MR imaging. DHEAS can be elevated in PCOS, as mentioned in the literature by several studies; for instance, Goodarzi and colleagues[96] reported that 20% to 30% of patients with PCOS have DHEAS excess. Some clinicians use a DHEAS cutoff of 700 ug/dL.[97,98] If the testosterone level is lower than 200 ng/dL, an ACTH stimulation test should be considered. If the stimulated 17OHP is lower than 1000 ng/dL, the etiology is PCOS or functional hyperandrogenism; whereas, for 17OHP levels higher than 1000 ng/dL, the diagnosis is the nonclassic form of 21-hydroxylase deficiency.[97,99–103] Of course, any clinically significant hyperandrogenism should be evaluated regardless of the absolute testosterone level.

Benign or malignant functioning adrenocortical tumors (see **Fig. 8**) typically cause hyperandrogenism but can also present with feminization.[97] Feminizing adrenal tumors are extremely rare, usually seen in men and children, and defined as adrenal neoplasms secreting estrogens with or without other adrenal gland hormones.[104]

SUMMARY

In conclusion, adrenal-related endocrine disorders are commonly encountered pathologies that require a detailed clinical, biochemical, and imaging workup. CT is the standard imaging method for adrenal gland pathologies. Ultrasonography can be considered in neonates and young children. MR imaging and nuclear medicine studies such as MIBG and gallium-68 DOTATATE PET are useful adjuncts to CT when CT is negative or inconclusive. The management of adrenal-related endocrine disorders is one that requires close collaboration and teamwork among endocrinologists, radiologists, and surgeons.

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