CME

Diagnosing and managing adrenal incidentalomas

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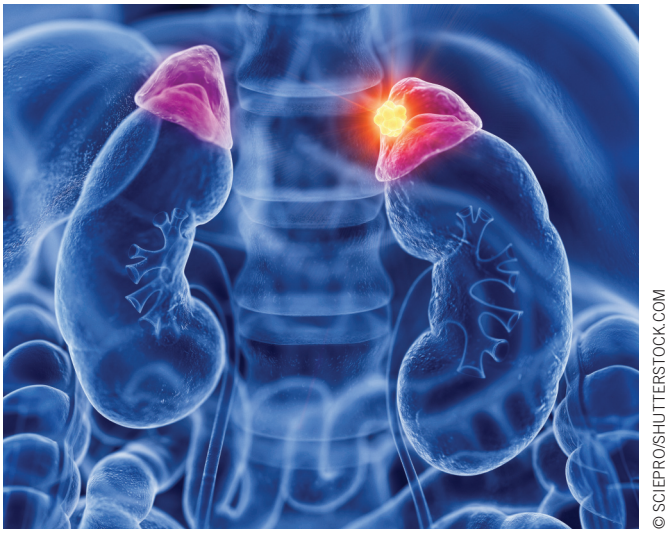
ABSTRACT

Adrenal incidentalomas are commonly encountered because of the widespread use of high-resolution cross-sectional imaging. Adrenal incidentalomas may be benign or malignant, and also may demonstrate hormonal hypersecretion, so all patients with adrenal masses should undergo further assessment. Clinicians should have a basic understanding of adrenal incidentalomas, their workup, and when follow-up and referral are warranted.

Keywords: adrenal mass, Hounsfield units, screening, subclinical Cushing disease, pheochromocytoma, hyperaldosteronism

Learning objectives

- Understand imaging characteristics that indicate the likelihood of malignancy or pheochromocytoma.
- Describe appropriate hormonal workup in patients with adrenal incidentalomas.
- Recognize when endocrine and/or surgical referral are warranted.
- Recognize which adrenal masses warrant follow-up imaging.



Adrenal incidentalomas are adrenal masses of 1 cm or larger that are discovered on cross-sectional imaging performed for nonadrenal disease indications.[1] High-resolution cross-sectional imaging of the abdomen has resulted in an increased frequency of detection of adrenal masses, with prevalence of 5% to 7% in adults; prevalence increases with age.[2,3] Unilateral incidentalomas are more frequently encountered, but incidentalomas can be bilateral in up to 20% of patients. Most adrenal masses are benign (85% to 95%) and nonfunctioning (50% to 70%).[1,4] Most benign adrenal tumors are adrenal cortical adenomas, which account for 80% to 85% of all cases.[5] Other benign masses include adrenal myelolipomas, cysts, ganglioneuromas, lymphangiomas, and hemangiomas.[6-8] Malignant lesions include adrenocortical carcinoma (0.3% of all adrenal masses), metastases/lymphomas (7.5% of all adrenal masses), and very rarely sarcomas or other malignant masses.[4,9] Factors associated with adrenal malignancy include age (under 18 years or over 65 years), larger size of the mass, bilateral adrenal masses, history of malignancy (increased risk of metastasis), and more than 20 Hounsfield units (measure of radiodensity on unenhanced CT scan).[4,5,10-12]

Only a minority of patients with adrenal masses undergo appropriate hormonal workup.[4,13,14] Notably, up to 50% of patients with adrenal incidentalomas demonstrate mild autonomous cortisol secretion (MACS). Less commonly, patients may present with overt cortisol excess (Cushing syndrome), catecholamine excess (pheochromocytoma), or aldosterone excess (primary aldosteronism).[5,15,16]

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Key points

- Adrenal incidentalomas are common and require hormonal and imaging workup.
- Measurement of Hounsfield units on unenhanced/noncontrast CT may assist in ruling out malignancy and can affect hormonal workup.
- Patients with nonfunctioning tumors with low Hounsfield units may not require longitudinal follow-up or intervention.

Two questions should be asked whenever an adrenal mass is encountered: Is it malignant? Is it functional? Clinicians need to be aware of the guidelines for workup and management of patients with adrenal incidentalomas, ensuring that proper treatment is pursued to avoid negative effects on patient morbidity and mortality. Without appropriate management, patients may develop resistant or difficult-to-control hypertension, chronic kidney disease, cardiovascular disease, bone loss, fractures, or diabetes.[1,2,5,16-19]

CLINICAL ASSESSMENT

A detailed medical history, family history, current medications (including over-the-counter medications), and physical examination for signs and symptoms of hormonal excess are important in assessing a patient with a newly discovered adrenal incidentaloma. Medical history should include history of hypertension, hyperlipidemia, type 2 diabetes, osteoporosis, cardiovascular events, and history of malignancy. For patients with comorbidities, document the date of diagnosis and the clinical course, noting whether the comorbidity was diagnosed close to the discovery of the adrenal mass, whether it was rapidly progressing, and number of medications needed to obtain control. Obtain a family history, including adrenal/endocrine disorders and genetic disorders that may be associated with more insidious pathologies (for example, multiple endocrine neoplasia type 2 and neurofibromatosis).[5]

Many patients who have an adrenal mass are asymptomatic. Clinical manifestations and comorbidities are summarized in **Table 1**.

EVALUATION OF MALIGNANCY

The imaging appearance of an adrenal mass may identify the cause; adrenal masses can additionally be categorized based on specific imaging features (unenhanced-CT Hounsfield units or chemical shift on MRI), size of the mass (larger than 1 cm but less than 4 cm versus 4 cm and larger), and growth of the mass over time if previous

TABLE 1. Clinical manifestations of adrenal masses based on hormone hypersecretion[1,5,18,24,30]

Hormone (clinical diagnoses)	Prevalence, symptoms, and comorbidities	Physical examination findings
Cortisol (mild autonomous cortisol secretion, Cushing syndrome)	• May be asymptomatic • Increased risk of hypertension, dyslipidemia, obesity, vertebral fractures, dysglycemia • Rarely presents with symptoms of overt Cushing syndrome (weight gain, muscle wasting, bruising)	• May not have physical examination findings • Central adiposity • Proximal muscle weakness • Striae (abdomen, axilla) • Moon facies • Dorsocervical fat pad
Aldosterone (primary hyperaldosteronism)	• About 10% of patients have secondary hypertension • Difficult to control BP on multiple antihypertensive drugs • Hypokalemia (40%) leading to fatigue, weakness, muscle cramps, and cardiac dysrhythmias (if severe) • Increased cardiometabolic risk	No specific physical examination findings other than hypertension
Catecholamines (pheochromocytoma)	• Up to 7% of adrenal incidentalomas, almost 60% are incidentally diagnosed • Most are discovered while asymptomatic • Hypertension most common (90%), can be paroxysmal (50%) • Pallor, headaches, sweating, palpitations • Hypertensive crisis (rare) because of other stressors (illness, surgery, medications); increased morbidity and death in this scenario	• May not have physical examination findings • Tachycardia • Resting tremor • Hypertension • Orthostatic hypotension • Symptoms of specific genetic disorders such as neurofibromas
Androgens (androgen-secreting adrenal tumors, congenital adrenal hyperplasia)	• Uncommon • Androgen excess is a common clinical presentation of adrenocortical carcinoma in women • No symptoms in men • Women may experience hirsutism, acne/oily skin, hair loss, menstrual irregularities, and infertility	• No findings in men • Findings in women may include acne, hirsutism (face, neck, chest, back, abdomen, inner thighs), male-pattern baldness, virilization

imaging is available for comparison. Initial evaluation for malignancy is centered on imaging adrenal masses, and specific characteristics of the adrenal masses can provide an understanding of the likelihood and risk of malignancy.[5,10,20-26] Unenhanced CT scan is the preferred imaging modality for adrenal masses because it can measure the mass's lipid content and provide Hounsfield units.[5] Hounsfield units less than 10 indicate with high specificity that the lesion is benign and additional imaging is not needed; this is a helpful measurement in terms of malignancy risk.[23,25] Other possible findings that may indicate a benign entity include homogenous appearance, smooth edges, lack of calcification, lack of vascularity, and smaller size (less than 4 cm), if no other worrisome characteristics are present.[10,14] MRI with chemical shift is a reasonable alternative, but it is not necessary to perform both an unenhanced CT and MRI with chemical shift; MRI is more expensive and is redundant if unenhanced CT has been completed. CT scan with absolute washout of greater than 60% and relative washout greater than 40% has been noted to have high sensitivity and specificity in differentiating lipid-poor adenomas from other adrenal masses on noncontrast imaging with high sensitivity and specificity. However, the accuracy of these thresholds were reported to be lower in a recent study.[27] In addition, adrenal masses such as pheochromocytoma can have a washout of greater than 60% in up to 33% of cases.[23,27] Ultrasonography is not indicated due to lower sensitivity and specificity. Imaging characteristics of adrenal masses are summarized in **Table 2**.[8]

Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan and adrenal biopsy should not be ordered routinely for assessment of adrenal masses. The use of FDG-PET scan is generally reserved for assessment of adrenal masses in patients with known primary malignancy and suspicion for metastatic disease in the adrenal glands.[23,27] Adrenal biopsy rarely is performed; its use is limited to patients with certain indeterminate adrenal masses, such as metastases, infiltrative diseases, and/or hemorrhage, where management would potentially be affected by the biopsy results. Pheochromocytoma should be ruled out before adrenal biopsy because significant hypertension may occur during biopsy. Adrenocortical carcinomas should not be biopsied routinely because of poor diagnostic accuracy and concern for needle track seeding.[1,5] We recommend that

TABLE 2. Imaging presentation and characteristics of adrenal masses[5]

	Adrenal adenoma and macronodular hyperplasia*	Other benign adrenal mass	Pheochromocytoma	Adrenocortical carcinoma	Other malignant masses
Tumor size Median (percentage less than 4 cm)	1.5 to 2.5 cm (95%)	2 to 3 cm (60% to 70%)	4 to 5 cm (45%)	10 cm (1% to 2%)	3 cm (60%)
Bilateral tumors	15% to 20%	5% to 10%	5% to 10%	<0.1%	24% to 43%
Tumor growth	<1 cm/yr	<1 cm/yr	<1 cm/yr	>1 cm/3 to 6 mo	>1 cm/3 to 6 mo
Unenhanced CT (Hounsfield units)					
Less than 10	50% to 60%	Variable depending on cause	0%	0%	0%
10 to 20	20% to 30%		1% to 3%	1% to 2%	1% to 4%
More than 20	10% to 20%		97% to 99%	98% to 99%	96% to 98%
Contrast washout	Fast (relative washout >40%, absolute washout >60%)	Variable	Slow	Slow	Slow
MRI					
Chemical shift present**	60% to 80%	Variable depending on cause***	0%	0%	0%
Chemical shift absent**	20% to 40%		100%	100%	100%

Adapted with permission from Bancos I, Prete A. Approach to the patient with adrenal incidentaloma. *J Clin Endocrinol Metab.* 2021;106(11):3331-3353.

*Adenomas can be functioning or nonfunctioning.
**Limitations in accuracy/interrater variability. When chemical shift is present, it excludes malignancy and pheochromocytoma.
***Myelolipomas, cysts, hematomas, ganglioneuromas, lymphangiomas, calcification, inflammatory disorder (sarcoidosis, Erdheim-Chester disease), or, rarely, infection (tuberculosis, histoplasmosis)

TABLE 3. Biochemical workup for adrenal masses[1,5,9,24,28,30,31]

	Whom to test	Screening test	Interpretation	Second-line testing	Notes
Mild autonomous cortisol secretion and Cushing syndrome	All patients with adrenal masses	• 1-mg dexamethasone suppression test • Baseline ACTH and dehydroepiandrosterone sulfate (DHEAS) test on a separate morning from dexamethasone suppression test	• Cortisol of 1.8 mcg/dL or less excludes cortisol excess • Cortisol of 1.9 to 5 mcg/dL suggests possible autonomous cortisol production • Cortisol greater than 5 mcg/dL is suggestive of autonomous cortisol production	• 8-mg dexamethasone suppression test • 24-hour urine for cortisol • Midnight salivary cortisols	Consider measuring dexamethasone levels if: • Discordant test results • Concern for compliance • Concern for absorption of dexamethasone
Primary hyperaldosteronism	History of hypertension and/or spontaneous hypokalemia	Morning renin and aldosterone	• Positive case detection: Aldosterone greater than 10 units and renin less than 1 unit and/or aldosterone:renin ratio greater than 20 • Confirmed if paired with spontaneous hypokalemia	24-hour urine for aldosterone with salt loading OR saline infusion test	Mineralocorticoid receptor antagonists (spironolactone, eplerenone) can affect test results (can lead to false-negative but not false-positive results)
Pheochromocytoma	All patients with adrenal mass(es) of 10 Hounsfield units or greater	Plasma metanephrines or 24-hour urine for metanephrines and catecholamines	Abnormal results usually more than twice the upper limit of normal (depends on tumor size)	None	• Plasma metanephrines have a false-positive rate of 17% • Multiple medications can affect the results
Adrenocortical carcinoma	• Consider in patients with unilateral adrenal mass of 10 or more Hounsfield units (usually more than 20) suspected as adrenocortical carcinoma • Patients with androgen excess	• Workup for cortisol and aldosterone excess • Androgen hormones in women (DHEAS test, testosterone, androstenedione)	Increased levels of steroid precursors (almost in 100%) • Elevated androgen levels (in 40%) • Combined adrenal hormone excess (such as cortisol and androgen excess) (in 30%)	24-hour urinary steroid metabolomics	Many are diagnosed incidentally
Congenital adrenal hyperplasia	All patients with bilateral adrenal masses	17-hydroxyprogesterone	Considered if levels above normal range	Possible stimulation testing with cosyntropin	In women, reference range varies by phase of menstrual cycle
Primary adrenal insufficiency	Patients with bilateral adrenal masses with possible symptoms (fatigue, nausea, vomiting, weight loss, hypotension)	Morning cortisol and ACTH	Elevated ACTH plus low cortisol, primary adrenal insufficiency likely (pending degree of abnormal tests)	• Cosyntropin stimulation testing • Renin • Aldosterone • Electrolytes	Low ACTH with low cortisol indicative of secondary adrenal insufficiency, unrelated to adrenal masses

TABLE 4. Management and referral considerations for adrenal masses[1,5,18,20,24,29,30,32,33]

Nonfunctioning adrenal adenoma smaller than 4 cm

- Patients who had appropriate initial workup do not require yearly monitoring
- Because 4% to 8% of patients may develop mild autonomous cortisol secretion, consider repeating dexamethasone suppression test 3 to 5 years after initial evaluation
- Consider repeat imaging and/or workup if patient has changes in symptoms (new symptoms of hormone excess, risk of less than 0.5%)

Nonfunctioning adrenal adenoma of 4 cm or larger

- Referral to endocrinology to discuss management and if follow-up is needed (for example, no follow-up would be needed for clear cysts or adrenal myelolipomas, but may be considered for other large benign tumors)

Confirmed/suspected autonomous cortisol production (mild autonomous cortisol secretion, Cushing syndrome)

- Referral to endocrinology and adrenal surgeon for adrenalectomy
- Patients may require a temporary hydrocortisone taper postoperatively pending postoperative cortisol testing/cosyntropin stimulation testing (around 50% risk)
- Management of comorbidities (hypertension, dyslipidemia, diabetes) after cure required because treatment strategies may change

Confirmed/suspected primary hyperaldosteronism

- If patients are looking for a surgical cure, adrenal vein sampling is required to confirm lateralization of aldosterone production, even in many patients with known adrenal masses
- If the adrenal vein sampling does not lateralize and/or the patient is not a surgical candidate, recommend treatment with aldosterone antagonists
  - Options include spironolactone and eplerenone
  - Monitor potassium levels and administer potassium replacement when needed
  - Eplerenone should be the first-line agent in men. Gynecomastia can occur with spironolactone in men; switch patients to eplerenone if this adverse reaction occurs.

Confirmed pheochromocytoma

- Referral to endocrinology and adrenal surgeon for adrenalectomy. Patients will require an alpha-blockade with doxazosin or phenoxybenzamine, possibly also with beta-blockade at least 7 to 14 days before surgery to reduce the risk for severe intraoperative hypertension.
- Refer patients for genetic testing (up to 50% risk of genetic association)

Indeterminate masses with negative biochemical workup, especially larger than 4 cm

- Refer patient to endocrinology for evaluation and consideration of adrenalectomy

Rapidly enlarging or new masses, high suspicion for malignancy, high suspicion for adrenocortical carcinoma

- Urgent referral to a multidisciplinary center with oncology, endocrinology, and/or surgery for management and consideration of further workup (such as a FDG-PET and adrenal biopsy for suspected metastasis). Adrenal biopsy should not be done in patients with adrenocortical carcinoma (poor accuracy, potential for seeding) or pheochromocytoma (risk of significant hypertension).

endocrinology and/or oncology clinicians determine if FDG-PET scan and/or adrenal biopsy are warranted for a patient.

In summary, all patients who are found to have an adrenal incidentaloma should undergo specific imaging of the adrenal mass as an initial step with unenhanced CT scan (preferred) or MRI with chemical shift (alternate) to help determine the risk of malignancy.[1,5]

BIOCHEMICAL EVALUATION

All patients with an adrenal mass of 1 cm or larger should be screened for hormonal hyperfunction, even if they are asymptomatic; patients with masses smaller than 1 cm should be screened if they have clinical signs and symptoms of hormone excess.[1] Hormonal hyperfunction, if present, can manifest as cortisol excess (MACS or Cushing syndrome), catecholamine excess (pheochromocytoma), aldosterone excess (primary hyperaldosteronism), or other rare presentations such as hyperandrogenism.[5]

Previously, guidelines recommended uniform workup for cortisol and catecholamine excess in all patients with adrenal incidentalomas; workup for primary hyperaldosteronism was reserved for patients with hypertension and/or hypokalemia.[1] Based on the most recent data, not all patients require testing for pheochromocytoma because it is extremely rare (less than 0.5% of cases) in those with benign imaging characteristics (Hounsfield units less than 10).[22,28] Additionally, some patients require additional workup if presenting with bilateral adrenal masses and/or signs and symptoms of primary adrenal insufficiency (**Table 3**). Refer patients who present with positive case detection testing to endocrinology.

MANAGEMENT AND REFERRAL

Management of adrenal incidentalomas varies depending on imaging characteristics and biochemical workup. Consider referring all patients with adrenal masses to endocrinology for initial assessment and workup. However, limited access to endocrinology and/or long wait times for appointments could be a limiting factor, so the patient's primary care provider may need to perform imaging and appropriate workup. If a patient with an adrenal mass of less than 10 Hounsfield units has a negative biochemical workup, repeat biochemical workup and imaging are not required, and the patient can be reassured that no further follow-up is needed unless new clinical signs of hormonal excess develop or comorbidities worsen.[5,18,24,29] For all other patients, referral and/or additional management is required. We recommend referring patients to an endocrinology clinician if the patient is a child or has:

- a lesion 4 cm or greater
- specific concerning findings on imaging such as inhomogeneity, irregular borders, or calcifications
- a lesion that increases in size over time

- bilateral adrenal masses
- an abnormal screening hormonal evaluation
- overt features of adrenal hormone excess on physical examination
- a personal history of malignancy
- a family history of endocrine tumors and/or genetic syndromes that are associated with adrenal masses.

A discussion of management and referral recommendations is detailed in **Table 4**.

CASE

A 58-year-old woman presents to your office concerned about an adrenal mass discovered incidentally. She was seen in the ED 2 days ago for abdominal pain. CT of the abdomen with contrast reported a 1.5-cm right adrenal mass, indeterminate but likely benign. Her past medical history includes hypertension treated with three antihypertensive drugs, dyslipidemia, obesity, and type 2 diabetes treated with basal insulin and metformin.

The patient had an unenhanced CT that confirmed a 1.5 cm mass with Hounsfield units of 3. Her cortisol level after 1-mg dexamethasone suppression test was less than 1 mcg/dL. Her aldosterone level was 8 ng/dL and renin level was 2 ng/mL/h, for an aldosterone:renin ratio of 4. She was reassured that the adrenal mass was benign and no further follow-up was needed.

CONCLUSION

Adrenal incidentalomas are commonly found in clinical practice and may lead to significant patient morbidity and even mortality, if malignant or hormonally active. Imaging characteristics, biochemical workup for hormonal hypersecretion, follow-up imaging, and/or referral are needed for all patients. Fortunately, half of all adrenal incidentalomas are benign and nonfunctional; therefore, limited or no follow-up is needed for patients who undergo an appropriate initial workup. **JAAPA**

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