67-Year-Old Woman With an Adrenal Mass

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A 67-year-old woman presented to the emergency department with a 2-day history of right-sided flank pain. A noncontrast abdominal computed tomography (CT) scan revealed a partially obstructing right ureteral calculus. Incidentally found on noncontrast CT was a 2.7-cm right-sided adrenal mass that measured 15 Hounsfield units (HU), appeared homogenous and round, had smooth borders, and did not have calcifications or necrotic areas. The patient had no prior cross-sectional imaging for comparison. She spontaneously passed the kidney stone, with resolution of her pain.

The following week, the patient presented to her internist concerned about the adrenal mass. She reported having no fevers, chills, night sweats, anorexia, headaches, palpitations, panic attacks, episodes of severe hypertension, abdominal pain, or easy bruising. She reported an intentional 10-lb. weight loss over the preceding year, which she achieved with diet and exercise. Her medical history is notable for Class II obesity, hyperlipidemia, well-controlled hypertension, well-controlled diabetes mellitus type 2 (DM2), and osteoporosis. Her medications included atorvastatin, hydrochlorothiazide, metformin, and once-yearly zoledronic acid. She had no personal or family history of malignancy or adrenal pathology.

Her vital signs were as follows: afebrile; heart rate, 91 beats per min; blood pressure, 118/76; respiratory rate, 15 breaths per min; oxygen saturation, 96% on room air; and body mass index, 36 kg/m^2. She appeared anxious but in no acute distress. She did not have a rounded face, dorsocervical fat pad, abdominal striae, evidence of hirsutism, ecchymoses, or thinning of skin. She had normal strength in her extremities, and the remainder of her neurologic examination was unremarkable. She had no palpable abdominal mass. Her ear, nose, and throat, lymphoid, cardiac, respiratory, and gastrointestinal examinations were unremarkable. A complete blood count, and her creatinine, sodium, and potassium levels were within normal limits.

1. Which *one* of the following is the *most likely* etiology of this patient's incidentally discovered adrenal mass?

a. Adrenal cortical adenoma (ACA)
b. Myelolipoma
c. Pheochromocytoma
d. Adrenal cortical carcinoma (ACC)
e. Adrenal metastasis

This patient presented with an adrenal incidentaloma (AI), which is defined as an adrenal mass that is unintentionally discovered on imaging obtained for an indication other than suspected adrenal pathology. Approximately 5% of all cross-sectional abdominal imaging results in the discovery of an adrenal mass.[1] The prevalence of adrenal masses increases with age, approaching 10% in the elderly.[2]

The differential diagnosis of AI is broad and includes benign and malignant etiologies. Approximately 92%-97% of AIs are benign.[3,4] Benign ACA is the most common etiology, with an estimated prevalence of 80% among all adrenal masses.[2] Adrenal myelolipomas are benign masses composed of hematopoietic cells and mature adipocytes; they comprised 8% of all AIs in a surgical series.[2]

Pheochromocytomas are a less common cause of AI, with an estimated frequency of 3%-5%,[3,4] and are typically benign, but 10% develop metastases. Other malignant etiologies of AIs include ACC, which has a frequency of approximately 1.9%-4.7%, and adrenal metastases, which have a frequency of approximately 0.7%-2.5%.[3,4] However, the prevalence of adrenal metastases is much higher in patients who have known extra-adrenal malignancy.[5]

For this patient, and for any patient with a newly diagnosed adrenal mass, it is essential to answer 2 questions: *Is the adrenal mass malignant?* and *Is the adrenal mass hormonally active?*

See end of article for correct answers to questions.

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The answer to these questions determines patient management and prognosis.

2. Which *one* of the following imaging findings would *best support* a diagnosis of a benign adrenal cortical adenoma in this patient?

a. HU less than 10 on noncontrast CT scan
b. Unchanged signal intensity on out-of-phase images compared with in-phase images on chemical shift magnetic resonance imaging (MRI)
c. High adrenal mass standard uptake value on fluoro-deoxyglucose positron emission tomography integrated with CT scan
d. A relative washout of less than 40% and an absolute washout of less than 60% on contrast-enhanced washout CT scan
e. Adrenal mass size of more than 4 cm

The vast majority of ACAs have a large intracellular lipid component.[6] In contrast, nearly all malignant adrenal lesions lack a substantial intracellular lipid component.[6] As lipid content increases, HU decrease; thus, many ACAs demonstrate HU less than 10 on unenhanced CT scan. For patients without extra-adrenal cancer, a threshold of more than 10 HU on noncontrast CT scan has a sensitivity for malignancy of 100% but a specificity of only 72%.[1]

On chemical shift MRI, the loss of signal intensity on out-of-phase images compared with in-phase images reflects a high lipid content of the lesion and supports a diagnosis of a benign adrenal mass.[5] However, up to 30% of benign ACAs are lipid poor, which limits the ability of chemical shift MRI to distinguish benign from malignant adrenal masses consistently.[1,6] A fluoro-deoxyglucose positron emission tomography integrated with CT scan is used to evaluate cellular uptake of deoxyglucose, which is a measure of tumor metabolic activity. A low adrenal mass standard uptake value supports a diagnosis of a benign mass. However, increased uptake is not specific for malignancy and is seen in other conditions of increased cellular metabolism, including pheochromocytoma and infection.

Benign ACAs demonstrate rapid intravenous (IV) contrast uptake and rapid IV contrast loss.[5] Malignant adrenal masses also typically demonstrate rapid IV contrast uptake but have slower IV contrast loss.[5] To predict malignancy, contrast-enhanced washout CT is used to calculate the relative and absolute loss of IV contrast from an adrenal mass.[5] On contrast-enhanced washout CT, a relative washout of more than 40% and an absolute washout of more than 60% suggest a benign adrenal mass.

Typically, malignant adrenal masses are larger in size than benign adrenal masses.[7] Yet, poor specificity limits the use of mass size to predict malignancy. In one study, a mass size threshold of 4 cm had a sensitivity of 81.3% but a specificity of only 61.4% in differentiating ACAs from non-ACAs.[8]

This patient's noncontrast abdominal CT scan revealed that her adrenal mass is less than 4 cm and lacks other imaging features associated with malignancy, including calcifications and necrotic areas. However, her adrenal mass is indeterminate because the HU were more than 10. The most likely etiology is a lipid-poor benign ACA, but a small ACC or other adrenal malignancy cannot be excluded.

3. Which *one* of the following adrenal hormone abnormalities is *most likely* to be present in this patient?

a. Catecholamine excess
b. Overt Cushing syndrome
c. Subclinical Cushing syndrome
d. Primary hyperaldosteronism
e. Sex hormone excess

More than 15% of all AIs are functional and release catecholamines, glucocorticoids, mineralocorticoids, and in rare cases, androgens or estrogens.[7] Approximately 3% of all AIs are pheochromocytomas.[3] This patient did not report the classic triad of pheochromocytoma, which includes headache, diaphoresis, and palpitations. However, approximately 75% of patients with a pheochromocytoma do not present with the classic triad. At least 10% of pheochromocytomas are discovered incidentally on imaging in the absence of any symptoms.[9] Patients diagnosed with an AI should undergo evaluation for pheochromocytoma by measurement of either urinary fractionated or plasma-free metanephrines.[5]

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Cortisol excess can present as overt Cushing syndrome, with classic features that include abdominal striae, proximal muscle weakness, spontaneous ecchymoses, and central obesity with peripheral muscle wasting. Yet, patients can have glucocorticoid secretory autonomy in the absence of overt Cushing features, which is known as subclinical Cushing syndrome (SCS). Potential manifestations of SCS include DM2, hypertension, and osteoporosis.[10] SCS is the most common etiology of hormonally active adrenal masses, and it is estimated to be present in at least one-third of patients who have an AI.[11]

This patient has potential manifestations of SCS, including Class II obesity, hypertension, hyperlipidemia, DM2, and osteoporosis. All patients with an AI, regardless of symptoms, should be tested for evidence of cortisol excess with a 1-mg overnight dexamethasone suppression test.[5]

Aldosterone-producing adenomas (APAs) comprise at least 1% of AIs and can present with hypertension or hypokalemia.[10] However, most patients who have primary hyperaldosteronism are not hypokalemic. This patient has a longstanding history of hypertension that appears to be well controlled on hydrochlorothiazide monotherapy. Her potassium level was within the reference range. Any patient with an AI and hypertension or unexplained hypokalemia should be evaluated for excess aldosterone production.[5] To test these patients, obtain a morning plasma aldosterone concentration and plasma renin activity level.

Elevated adrenal sex hormone production raises the possibility of ACC, especially in the setting of hypercortisolism. However, patients who have an AI do not require routine testing for sex hormone—producing masses. Sex hormone levels can be measured in patients who have signs or symptoms of androgen excess or an adrenal mass with imaging features that are concerning for ACC.[5]

For this patient, a 1-mg overnight dexamethasone suppression test was performed, and results were abnormal, with a serum morning cortisol value (reference ranges provided parenthetically) of 6.2 μg/dL (<1.8 μg/dL). Although the threshold of 1.8 μg/dL has low specificity, this indicates autonomous cortisol secretion and, in the absence of overt Cushing syndrome features, was concerning for SCS. A basal morning plasma adrenocorticotropic hormone level was low at 9 pg/mL (10-60 pg/mL), and a 24-hour, urinary free cortisol level was high-normal at 37 mcg/24 hours (3.5-45 mcg/24 hours), further supporting the diagnosis of SCS. Plasma-free metanephrines, plasma aldosterone concentration, and plasma renin activity were also measured and found to be normal.

4. Which *one* of the following statements regarding this patient is *most accurate*?

a. She is at high risk for progression to overt Cushing syndrome
b. The prevalence of hypertension is similar in patients who have SCS, compared with patients who have a nonfunctional adrenal mass
c. Cardiovascular event risk is similar in patients who have SCS, compared with patients with a nonfunctional adrenal mass
d. Consideration should be given to adrenalectomy
e. Conservative management and adrenalectomy are equally effective at improving glycemic control

Less than 1% of patients who have SCS progress to overt Cushing syndrome.[5] Yet, SCS is still associated with significant morbidity and mortality. Hypertension, DM2, dyslipidemia, and obesity are more prevalent in patients who have SCS than in those who have nonfunctional adrenal masses.[11] Further, cardiovascular event risk is higher in patients who have SCS compared with those who have nonfunctional adrenal masses.[11]

Nevertheless, clear guidelines are lacking regarding if and when to perform adrenalectomy in SCS, which means the decision to perform surgery is highly individualized. The 2016 European Society of Endocrinology's (ESE) guidelines recommend that adrenalectomy be considered in patients who have autonomous cortisol secretion, even in the absence of comorbidities that are likely secondary to hypercortisolism.[5] The ESE suggests that patient demographics, degree of cortisol production, comorbidities, and goals of care should guide decision making regarding the need for adrenalectomy.[5]

Patients who have SCS and undergo adrenalectomy have greater improvement in hypertension and glycemic control compared with patients who are treated with conservative management alone.[11] However, adrenalectomy was not superior to conservative therapy in the management of dyslipidemia or obesity.[11]

Given this patient's indeterminate imaging characteristics, biochemical evidence of autonomous cortisol production, and comorbidities of Class II obesity, hyperlipidemia, hypertension, DM2, and osteoporosis, adrenalectomy was discussed. Ultimately, she declined adrenalectomy, due to a strong preference to avoid surgery.

5. Given her preference to avoid surgery, which *one* of the following is the *most appropriate* management strategy for this patient?

a. Biopsy of the adrenal mass
b. Screen for an asymptomatic vertebral fracture
c. No further follow-up is required for the adrenal mass
d. Repeat a noncontrast CT abdominal scan in 2 years
e. Repeat biochemical assessment for cortisol excess every 6 months for the next 3 years

The rate of a nondiagnostic adrenal biopsy is 8.7%, and the sensitivity of detecting ACC with an adrenal biopsy is only 70%.[12] An adrenal biopsy is unnecessary if the AI has benign imaging characteristics and the patient has no history of extra-adrenal malignancy.[5] Given that this patient has no history of malignancy, and her adrenal mass is likely a benign lipid-poor ACA, a biopsy is not indicated.

Subclinical Cushing syndrome is a risk factor for vertebral fracture.[5] The 2016 ESE guidelines suggest baseline screening for vertebral fracture with a plain radiograph, even if the patient is asymptomatic.[5] For this patient, a screening radiograph was performed and was negative for fracture.

Although the adrenal mass is less than 4 cm in this patient and has multiple benign imaging features, it measures more than 10 HU and thus is considered indeterminate for malignancy. Therefore, follow-up with serial monitoring is essential. The 2016 ESE guidelines suggest repeat imaging with a noncontrast CT scan or MRI after 6-12 months for patients with indeterminate adrenal masses who forgo adrenalectomy at baseline, in order to diagnose malignant tumors that may have initially presented as indeterminate masses.[5]

A yearly clinical assessment is recommended in patients who have SCS, to evaluate for manifestations of cortisol excess.[5] If development or interval worsening of comorbidities thought to be secondary to hypercortisolism occurs, a repeat biochemical evaluation should be performed.[5]

For this patient, a repeat noncontrast CT scan of the abdomen will be obtained in 12 months. She will be closely monitored by her general internist for management of her multiple comorbidities. She has follow-up endocrine assessment planned after her CT scan, at which point consideration will be given to repeating a biochemical evaluation to assess the degree of cortisol production, and the potential benefits of adrenalectomy will be readdressed.

DISCUSSION

An AI is an adrenal mass that is inadvertently discovered on imaging in a patient who is not suspected to have adrenal pathology. Given that the prevalence of AI is approaching 10% in the elderly, it is essential that internists be familiar with its diagnostic evaluation and management.[2]

More than 97% of AIs are benign, and ACA is the most common etiology.[3] Malignant adrenal masses include mostly ACC, and rarely adrenal metastases, sarcomas, or lymphomas. The initial workup of a patient who has an AI should aim to establish whether the mass is malignant and/or hormonally active. Several imaging modalities can be used to evaluate an AI, but a noncontrast CT scan is particularly valuable. A threshold of more than 10 HU on a noncontrast CT scan has a sensitivity of 100% for diagnosing malignancy in patients who have no known extra-adrenal cancer, but it has lower specificity because some benign ACAs are lipid poor.[1] A threshold of adrenal mass size more than 4 cm has a sensitivity of 81.3% in

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differentiating ACAs from non-ACAs, but it also has poor specificity.[7,8]

As many as 15% of AIs occur with overt manifestations of hormone excess.[7] Generally, all patients who have AIs should undergo evaluation for pheochromocytoma, by measurement of urinary-fractionated or plasma-free metanephrines, and for cortisol excess, with a 1-mg overnight dexamethasone suppression test.[5] Any patient with an AI and hypertension or unexplained hypokalemia should be tested for an aldosterone-producing adenoma, with plasma aldosterone concentration and plasma renin activity level tests.[5] Adrenal sex hormone levels can be obtained for patients who have signs or symptoms of androgen excess or an adrenal mass with imaging features that are concerning for ACC.[5]

Subclinical Cushing syndrome is a state of glucocorticoid secretory autonomy without overt features of Cushing syndrome; it is present in at least one-third of patients who have an AI.[11] Fortunately, less than 1% of patients who have SCS progress to overt Cushing syndrome.[5] However, patients who have SCS have a higher prevalence of hypertension, DM2, dyslipidemia, and obesity, and they have an increased risk for cardiovascular events and mortality compared with patients who have nonfunctional adrenal masses.[5]

Nevertheless, clear guidelines are lacking regarding if and when to perform adrenalectomy in patients who have SCS, mainly because therapeutic response to surgery varies.[11] Consequently, the decision to proceed with surgery is highly individualized and depends on the patient's preference, the degree of cortisol production, and the presence of comorbidities attributable to hypercortisolism. All patients who have SCS should undergo baseline screening for asymptomatic vertebral fractures.[5] Further, patients who have SCS who did not undergo adrenalectomy require yearly clinical assessments to evaluate for development or progression of comorbidities potentially attributable to hypercortisolism.

Patients with indeterminate adrenal masses on noncontrast CT or MRI require additional testing to clarify the etiology of the lesion. Either immediate additional imaging should be obtained, or if suspicion for malignancy is lower, repeat imaging with noncontrast CT or MRI can be done after 6-12 months.[5]

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CORRECT ANSWERS: 1. a. 2. a. 3. c. 4. d. 5. b.