Incidentally discovered adrenal masses ("adrenal incidentalomas") are found on approximately 2% to 3% of imaging studies performed for reasons other than suspicion of adrenal disease. The appropriate evaluation and management of adrenal incidentalomas is challenging. Most adrenal incidentalomas are benign and do not produce a hormonal syndrome. It is important to avoid unnecessary testing with its attendant costs and risks to the patient. At the same time, determining which masses represent functional adrenal tumors or malignancies is critical. Careful diagnostic evaluation is necessary to identify the likely pathologic entity so that appropriate treatment can be provided.

**CASE STUDY**

**Initial Presentation**

A 47-year-old woman presents to an endocrinologist with a 3-cm left adrenal mass that was discovered on abdominal computed tomography (CT) performed when she was passing a kidney stone.

**History**

The patient has had a 35-lb weight gain over the past year, worsening control of chronic hypertension, and increased peripheral edema. She developed hypokalemia, with values as low as 3.1 mEq/L, while using hydrochlorothiazide for her hypertension, and is now on a potassium supplement. Her other medications include olmesartan and sustained-release metoprolol. Her hypertension has been somewhat labile with occasional diastolic blood pressure readings above 100 mm Hg. She has had headaches and episodes of tachycardia with heart rates up to 180 bpm, but no unexplained sweats. She reports fatigue, muscle aches, and weakness. She denies easy bruising, menstrual irregularity, hirsutism, fractures, or loss of height. In addition to nephrolithiasis, her past history is significant for a melanoma, stage unknown, removed 8 years ago.

From North Shore Medical Center, Salem, MA.
ADRENAL INCIDENTALOMAS

Physical Examination
The patient weighs 192 lb and has a body mass index of 32 kg/m². Blood pressure is 150/95 mm Hg and heart rate is regular at 64 bpm. There are no murmurs or gallops. She has a round face but no plethora, no increased supraclavicular or cervicodorsal fat pads, and no hirsutism. Her abdomen is obese without masses or striae. She has normal muscle mass, with possible mild proximal lower extremity muscle weakness. There is 1+ pedal edema and no tremor.

Imaging Studies
The CT scan from the outside hospital shows a round, smooth, homogeneous adrenal mass measuring 6 Hounsfield units on an unenhanced study. There is no evidence of residual nephrolithiasis. A CT scan of the abdomen done 15 years ago is not available, but an adrenal mass was not mentioned in the report.

Laboratory Evaluation
Laboratory data obtained prior to the visit reveal sodium, 141 mEq/L; potassium, 4.4 mEq/L; chloride, 103 mEq/L; bicarbonate, 27 mEq/L; blood urea nitrogen, 22 mg/dL; creatinine, 0.9 mg/dL; and glucose, 94 mg/dL.

- What are the possible etiologies of a clinically inapparent adrenal mass?

The most common adrenal mass is a benign adrenal adenoma. In autopsy series, adrenal adenomas have a prevalence of 1.4% to 8.7%. The higher prevalence figures included adenomas as small as 0.2 cm [1]. Small, as well as large, adenomas may be hyperfunctioning.

Cortisol-producing adenomas are another category of incidentalomas. Using stringent criteria, dexamethasone suppression testing suggests that 2% to 12% of adrenal incidentalomas hypersecrete cortisol at presentation. Among adenomas initially considered nonfunctioning, approximately 1% to 2% will come to manifest cortisol hypersecretion if followed for up to 3 years [2]. Almost all of the adenomas that subsequently hypersecreted cortisol were 3 cm or larger in diameter at the initial evaluation. Adenomas that hypersecrete mineralocorticoid (eg, aldosterone) comprise only about 1% to 3% of clinically unsuspected adrenal masses. Pheochromocytoma has generally been found in 1.5% to 9% of incidentalomas but accounted for 23% in a Japanese series of 210 incidentalomas [3].

Adrenocortical carcinoma is rare based on data from tumor registries (annual incidence of 1 per 600,000 in the United States), yet it has been reported to represent approximately 5% of incidentalomas. Much of these data come from surgical series where there may be an ascertainment bias. Also, the higher prevalence of adrenocortical carcinoma among incidentalomas may reflect the slow growth of many of these cancers. While there is no absolute minimal size for adrenocortical carcinoma, all of those reported have had a diameter greater than 1 cm. Although the median 5-year survival for symptomatic adrenocortical carcinoma is only 35% [3], it may take several years before symptoms become manifest. Cancers that have been inadvertently followed rather than removed have been observed to only double in diameter during a 7-year interval [5].

Malignancies commonly metastasize to the adrenal gland. The most common primary sites are lung, breast, melanoma, stomach, kidney, pancreas, and colon. However, even in patients with known malignancies, almost half of adrenocortical incidentalomas are benign adenomas.

Pseudoadrenal masses also need to be considered. These masses may appear to be within the adrenal gland on the CT scan but actually arise in other organs such as kidney, pancreas, spleen, stomach, liver, lymph nodes, or blood vessels.

Systemic illnesses may manifest in the adrenal gland. Granulomas occur in tuberculosis and histoplasmosis. Adrenal cysts are seen in cryptococcosis, echinococcosis, and paragonimiasis. The cysts of paragonimiasis can be filled with creamy material and appear solid on CT scan [6]. Adrenal hemorrhage can be associated with trauma, sepsis, hypotension, or anticoagulation.

Several inherited disorders have an increased frequency of adrenal masses. Adrenal pheochromocytoma is associated with multiple endocrine neoplasia types 2A and 2B, paraganglioma/pheochromocytoma syndrome types 1 and 4, neurofibromatosis type 1, and von Hippel-Lindau disease [7]. Congenital adrenal hyperplasia frequently spurs an adrenocortical adenoma and, less commonly, bilateral nodular adrenals or adrenocortical carcinoma [8]. Other etiologies of adrenal masses are listed in Table 1.

- What is the approach to the clinical evaluation?

There are 4 main questions that should be answered by the clinical evaluation: (1) Is the mass hormonally active and likely to produce significant problems? (2) Is it a nonadrenal or metastatic malignancy requiring removal or confirmation for treatment planning? (3) Is it a granulomatous or cystic manifestation of an infectious disease? (4) Is it a primary adrenal malignancy? An approach to the workup is shown in the Figure.

The initial step is the history and physical examination.
Historical data obtained should include symptoms and signs of hypercortisolism (eg, weight gain, abnormal fat distribution, hypertension, glucose intolerance, striae, muscle wasting, osteopenia, depression), hyperaldosteronism (eg, hypertension, weakness), virilization (eg, hirsutism, clitoromegaly) or feminization (eg, gynecomastia), and catecholamine excess (eg, hypertension, tachycardia, palpitations, headache, sweats). Since benign adenomas are more common with aging, masses in younger patients (eg, <50 years) should be viewed with greater suspicion. An adrenocortical carcinoma may be associated with symptoms related to local extension (eg, back pain) or invasion into the vena cava. Adrenocortical carcinomas can cause symptoms by distant metastases, most commonly to the lung, liver, lymph nodes, peritoneum, bone, and pleura. Infectious etiologies, hemorrhage, and large benign masses (eg, myelolipoma) can also cause local pain. Bilateral destructive lesions can cause adrenal insufficiency. Any patient with significant clinical findings should be investigated thoroughly, as if the clinical concerns rather than the incidentaloma had prompted the evaluation [9].

- What features on imaging can help characterize the mass?

**Computed Tomography**

A CT scan is the most common initial study in which an adrenal mass in incidentally discovered. Review of this study and any previous studies that might be available should be done. Stability of the mass for at least 6 months, preferably for 18 months, generally reflects a benign process. Attenuation, measured in Hounsfield units (HU), may be defined for a designated region of interest within the mass. The region of interest for the CT density measurements should cover approximately one half to two thirds the size of the mass. Too large an area might include adjacent fat. Too small an area might lead to pixel sampling errors and may not reflect the true density of the whole lesion [10]. On an unenhanced CT scan, low attenuation within the mass suggests lipid content. The cells of cortical adenomas generally contain much intracytoplasmic lipid. The attenuation is even lower in fat-containing masses such as lipomas or myelolipomas.

Most often, the study on which an incidentaloma is found has been performed with intravenous contrast. Distinguishing benign adenomas from nonadenomas is not as reliable on a contrast study as it is on an unenhanced study. CT density considerations assume measurement within a relatively homogeneous mass. The cause of any heterogeneity must be considered. For example, areas of hemorrhage may produce increased density within an otherwise lipid-containing mass. Conversely, on rare occasions, malignancies can contain areas of fat or arise alongside a benign lesion, thereby creating a “collision tumor.”

If an unenhanced CT scan is available, the distinction is better. Homogeneous masses with CT attenuation less than 2 HU may be considered benign adenomas (or, occasionally, simple cysts or lipomas). An unenhanced CT attenuation greater than 43 HU generally represents a lesion other than an adenoma [11]. While homogeneity is generally a favorable sign, benign adenomas can undergo cystic degeneration and show heterogeneity. Also, rare homogeneous low-density adrenocortical carcinomas have been reported, but these

### Table 1. Etiologies of Adrenal Masses

<table>
<thead>
<tr>
<th>Adrenal cortex</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Metastasis</td>
</tr>
<tr>
<td>Adrenocortical-pituitary hybrid tumor</td>
<td></td>
</tr>
<tr>
<td>Nodular hyperplasia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adrenal medulla</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Malignant pheochromocytoma</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>Malignant ganglioneuroma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other neoplasms</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>Malignant neurofibroma</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>Malignant schwannoma</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Teratocarcinoma</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>Fibrous histiocytoma</td>
</tr>
<tr>
<td>Adenomatoid tumor</td>
<td></td>
</tr>
<tr>
<td>Myelolipoma</td>
<td></td>
</tr>
<tr>
<td>Lipoma</td>
<td></td>
</tr>
</tbody>
</table>

| Infectious              |                 |
|-------------------------|                 |
| Echinococcosis          |                 |
| Cryptococcosis          |                 |
| Paragonimiasis          |                 |
| Granuloma               |                 |

| Other                   |                 |
|-------------------------|                 |
| Cyst                    |                 |
| Hematoma                |                 |
| Amyloidosis             |                 |
| Extramedullary hematopoiesis |             |
| Xanthoma                |                 |
Incidentally discovered adrenal mass

Endocrine screening (see Table 2)

Nonfunctioning mass

Hormonally active mass

Unenhanced CT

Homogeneous

< 2 HU

< 3 cm

Annual clinical evaluation × 4 yr

3–6 cm

Annual hormonal evaluation × 4 yr

> 6 cm

Decisively benign imaging? (consider PET, NP59)

Heterogeneous or ≥ 2 HU

≤ 6 cm

CT washout

≥ 38% RPW or ≥ 52% APW

Mass size? (consider FNA)

< 3 cm

≤ 3 cm

Annual hormonal evaluation × 4 yr plus imaging at 6–12 mo

≥ 3 cm

Annual hormonal evaluation × 4 yr plus imaging at 6–12 mo

Yes

No

Surgery

Yes

Yes

Surgery

Indeterminate

Annual hormonal evaluation × 4 yr plus imaging at 3, 6, & 18 mo

Probable benign imaging? (consider PET, NP59)

Probably benign?

Other primary malignancy? (consider FNA, csMRI, PET, NP59)

Endocrine screening (see Table 2)

Unenhanced CT

Homogeneous

< 2 HU

< 3 cm

Annual clinical evaluation × 4 yr

3–6 cm

Annual hormonal evaluation × 4 yr

> 6 cm

Decisively benign imaging? (consider PET, NP59)

Heterogeneous or ≥ 2 HU

≤ 6 cm

CT washout

≥ 38% RPW or ≥ 52% APW

Mass size? (consider FNA)

< 3 cm

≤ 3 cm

Annual hormonal evaluation × 4 yr plus imaging at 6–12 mo

≥ 3 cm

Annual hormonal evaluation × 4 yr plus imaging at 6–12 mo

Yes

No

Surgery

Yes

Yes

Surgery

Indeterminate

Annual hormonal evaluation × 4 yr plus imaging at 3, 6, & 18 mo

Probable benign imaging? (consider PET, NP59)

Probably benign?

Other primary malignancy? (consider FNA, csMRI, PET, NP59)

Figur**e. Management of an incidentally discovered adrenal mass. APW = absolute percentage washout; csMRI = chemical shift magnetic resonance imaging; CT = computed tomography; FNA = fine-needle aspiration biopsy; HU = Hounsfield units; NP59 = iodocholesterol scintigraphy; PET = positron emission tomography; RPW = relative percentage washout.

Presented with syndromes of hormonal hypersecretion [12]. Special caution should be exercised to distinguish a simple cyst from a pseudocyst [13]. Pseudocysts may form within adrenal masses, including pheochromocytomas, functional adenomas, and adrenocortical carcinomas.

While the criterion of less than 2 HU provides nearly 100% specificity for a benign mass [14], only 47% of adenomas fall below this CT density. A widely accepted threshold is less than 10 HU. This criterion provides 96% to 98% specificity and encompasses 71% to 79% of benign masses [15,16]. Although the 10 HU criteria has been generally accepted, the lower specificity should be gauged with caution and masses in the 2 to 10 HU range deserve special scrutiny for other characteristics, such as homogeneity [17]. Irregular borders should be viewed with particular suspicion in any mass [18].

Even better distinctions can be made using delayed contrast-enhanced CT scans. This “washout” technique taps the observation that contrast washes out more rapidly from adenomas than from malignant lesions. With this approach, images are obtained at peak dynamic phase (“enhanced scan”) and again at 10 minutes (some centers use 15 minutes) after intravenous contrast (“delayed enhanced
The percent washout of enhancement relative to the initial enhancement is calculated as (dynamic HU – delayed HU/dynamic HU) × 100. A relative percentage washout of less than 38% has 100% sensitivity and 95% specificity for identifying metastatic lesions [11]. If an unenhanced scan is done, an absolute percent washout also can be calculated (dynamic HU – delayed HU/dynamic HU – unenhanced HU) × 100. The absolute percent washout is more accurate for benign masses that do not enhance much [19], such as an organized hematoma. The threshold for absolute percent washout is 52% [11]. This washout approach similarly distinguished between adrenocortical carcinoma and adenoma [20,21], although washout in the adenoma range has been reported in a well-differentiated carcinoma [22]. Also, pheochromocytomas may show substantial washout of contrast [23], but these masses should be distinguished by the hormonal evaluation.

The intravenous contrast washout approach may be used at the initial CT study in a well-informed radiology department. The technician can view the CT scan before the patient leaves the table. If an adrenal mass is detected, a delayed enhanced scan can be performed.

- What endocrine screening should be done?

The 2002 National Institutes of Health (NIH) consensus conference statement recommends screening all patients for pheochromocytoma with plasma free metanephrines and for hypercortisolism with a 1-mg overnight dexamethasone suppression test [24]. They make an exception for patients with imaging characteristics of a myelolipoma (here again, a collision tumor needs to be considered [25]) or an “adrenal cyst” (ie, a simple cyst, not a cystic tumor).

**Pheochromocytoma**

Pheochromocytomas represent approximately 3% of incidentally discovered adrenal masses. Approximately 90% of these patients have a history of hypertension or paroxysmal symptoms. Others may have pheochromocytomas that are clinically silent but potentially lethal. Autopsy series show approximately 50% of patients with pheochromocytoma do not have a recorded history of hypertension [26].

Although detection of pheochromocytoma is of utmost importance, should all patients with adrenal incidentalomas be screened? Pheochromocytomas are not low-attenuation tumors on CT scans. Except for cystic or fat-containing regions, pheochromocytomas are at least 2 HU on unenhanced CT scans [23]. Therefore, patients with homogenous adrenal incidentalomas less than 2 HU should not require screening. Caution should be exercised in reviewing the CT scan because cystic fluid can represent the majority of a pheochromocytoma with the tumor tissue appearing only as an outer rim. Since the false-positive rate for plasma free metanephrines is 11% to 18%, judicious use of screening can prevent engendering unnecessary follow-up testing.

Tests for plasma free metanephrines are more sensitive than 24-hour urine tests [27]; however, the specificity of urinary metanephrines was greater than that of plasma free metanephrines among patients with sporadic (nonhereditary) pheochromocytoma (89% versus 82%). Using fractionated urinary metanephrines improved sensitivity over total urinary metanephrines [28]. If the patient has paroxysmal symptoms, yield is improved if the 24-hour urine collection is initiated at the time of symptoms. In summary, if high sensitivity is desired, plasma free metanephrines are preferred; if higher specificity is desired, urinary fractionated metanephrines are advantageous.

**Cortisol Excess**

With regard to evaluation of cortisol excess, patients with even mild symptoms or signs of hypercortisolism that might be expected to improve after resection of an adenoma merit screening. Studies, albeit uncontrolled, have shown a variety of improvements after resection of adenomas that hypersecrete cortisol. These patients with “subclinical Cushing’s syndrome” showed reductions in blood pressure, weight, and glucose intolerance after surgical removal of the adenoma [29,30]. The term “subclinical autonomous glucocorticoid hypersecretion” (instead of subclinical Cushing’s syndrome) avoids the perspective that elevated cortisol needs to cause the full spectrum of Cushing’s syndrome [24]. Additionally, screening is valuable to identify cortisol excess stemming from a possible adrenocortical carcinoma.

The NIH-recommended test is a 1-mg overnight dexamethasone suppression test [24]. With this test, the traditional cutoff for an abnormal morning serum cortisol is greater than 5 µg/dL. Patients with clinical Cushing’s syndrome, however, have had values as low as 1.8 µg/dL [31,32]. Since the clinical concern in the setting of an incidentaloma is for corticotropin (ACTH)–independent Cushing’s syndrome, rather than pituitary Cushing’s disease, some researchers have advocated the use of 3 mg [33] or 8 mg dexamethasone [34]. Alternative tests, yet to be validated for adrenal incidentalomas, include bedtime (or “midnight”) salivary cortisol. Salivary cortisol has superior predictive value compared with the 1-mg overnight dexamethasone suppression test for Cushing’s syndrome that has presented clinically [35]. While there is no published study of bedtime salivary cortisol in incidentaloma patients, elevated midnight serum cortisol was associated with higher systolic blood pressure and fasting glucose concentrations [36].

Although 24-hour urinary free cortisol generally has
lower sensitivity than the overnight dexamethasone suppression test, it may have a special role to detect adrenal adenomas with abnormal receptors, such as for gastric inhibitory polypeptide that causes “food-dependent Cushing’s syndrome.” These tumors intermittently hypersecrete cortisol, and an integrated measure is more sensitive than one based on diurnal variation [37]. Incidentalomas with these aberrant receptors have been reported [38,39]. Suppressed morning ACTH levels have not been as uniformly observed as might be anticipated in the setting of an autonomous cortisol-secreting adenoma. ACTH levels in the normal range have been observed in 28% of clinically evident ACTH-independent Cushing’s syndrome [40]. In 1 study of adrenal incidentalomas, among patients defined as having subclinical Cushing’s syndrome by a postovernight 1-mg dexamethasone suppression test cortisol of greater than 3 μg/dL, only 44% had suppressed ACTH levels, whereas 79% had loss of diurnal cortisol rhythm [41]. In summary, the current recommendations for screening include fractionated plasma free metanephrines or 24-hour urinary fractionated metanephrines, but this recommendation may be modified when the CT image is incompatible with pheochromocytoma. The other recommended screening test is an overnight 1-mg dexamethasone suppression test, but depending on the criterion used, this test lacks adequate sensitivity or specificity; other tests of cortisol hypersecretion (bedtime salivary cortisol and 24-hour urinary free cortisol) may be used selectively. The suggested endocrine screening is summarized in Table 2.

Table 2. Endocrine Screening

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma (all patients, possible exception if unenhanced CT scan is homogeneous and density &lt; 2 HU)</td>
<td>Fractionated plasma free metanephrines or urinary fractionated metanephrines</td>
</tr>
<tr>
<td>Cortisol excess (all patients)</td>
<td>Overnight 1-mg dexamethasone suppression test</td>
</tr>
<tr>
<td>Mineralocorticoid excess (patients with hypertension)</td>
<td>Serum potassium and plasma aldosterone to plasma renin activity ratio</td>
</tr>
</tbody>
</table>

CT = computed tomography; HU = Hounsfield units.

Although CT scan is the most common study for initial detection of an adrenal mass, other imaging modalities, such as ultrasound or magnetic resonance imaging (MRI), may find an adrenal incidentaloma. Nuclear scintigraphy and positron emission tomography (PET) have roles in the further evaluation of uncharacterized masses.

Ultrasound

Ultrasound may be the initial study in which an adrenal mass is detected. Ultrasound typically misses smaller masses. In one study, ultrasound detected only 65% of tumors smaller than 3 cm seen on CT [45]. The adrenal gland may be seen especially well in thin patients but not in very obese patients. Ultrasound is useful in characterizing a cyst. A thin-walled, round, homogeneous fluid density lesion is consistent with a benign cyst.

Magnetic Resonance Imaging

With increased use, MRI is detecting more adrenal masses. Pheochromocytomas and adrenocortical carcinomas generally have high signal intensity on T2-weighted images, but values can overlap benign adenomas [46]. Chemical shift MRI enables better distinction. Chemical shift MRI gauges intracellular lipid, conceptually similar to the impact of lipid on CT attenuation. Chemical shift MRI uses the difference in resonance frequency between the protons of lipid and water. Unlike conventional spin-echo MRI, which places a refocusing pulse at the midpoint between the excitation pulse and the measurement time, chemical shift MRI moves the refocusing pulse so that lipid and water magnetization

- What is the role for other imaging techniques?

The clinical concern for patients with hypertension and an adrenal adenoma is for mineralocorticoid excess. Hyperaldosteronism is rarely a sole manifestation of adrenocortical carcinoma [42]. Patients should be screened with a serum potassium level and a plasma aldosterone concentration (PAC)–plasma renin activity (PRA) ratio. The NIH consensus conference recommended criteria for further evaluation of aldosterone excess were a PAC-PRA ratio greater than 30 (PAC in ng/dL and PRA in ng/mL/hr) coupled with a PAC greater than 18 ng/dL [24]. A positive screening test should be evaluated further with suppressive tests [43]. Spontaneous hypokalemia is found in about 75% to 80% of patients with aldosteronomas. The sensitivity of a low serum potassium level may be increased to greater than 90% if performed after 3 days of ingesting more than 200 mmol of sodium per day [44]. Hypokalemia may also help to signal mineralocorticoid excess other than aldosterone (eg, deoxycorticosterone).

- What additional endocrine screening should be done in patients with hypertension?

The clinical concern for patients with hypertension and an adrenal adenoma is for mineralocorticoid excess. Hyperaldosteronism is rarely a sole manifestation of adrenocortical carcinoma [42]. Patients should be screened with a serum potassium level and a plasma aldosterone concentration (PAC)–plasma renin activity (PRA) ratio. The NIH consensus conference recommended criteria for further evaluation of aldosterone excess were a PAC-PRA ratio greater than 30 (PAC in ng/dL and PRA in ng/mL/hr) coupled with a PAC greater than 18 ng/dL [24]. A positive screening test should be evaluated further with suppressive tests [43]. Spontaneous hypokalemia is found in about 75% to 80% of patients with aldosteronomas. The sensitivity of a low serum potassium level may be increased to greater than 90% if performed after 3 days of ingesting more than 200 mmol of sodium per day [44]. Hypokalemia may also help to signal mineralocorticoid excess other than aldosterone (eg, deoxycorticosterone).
is 180 degrees out of phase. The resulting pixel brightness is the net difference between lipid and water magnetization. The signal intensity loss is maximal when content is equal. Comparison is best made with a nonlipid-containing organ such as the spleen. The presence of lipid in the adrenal mass can be defined quantitatively by an adrenal to spleen ratio, defined as the percentage of signal remaining in the opposed-phase image relative to the in-phase image. Ratios less than 70 are associated with benign adenomas. Several studies also show the reliability of qualitative visual inspection of the change in signal intensity within the mass. Lipid-poor adenomas pose a problem for the sensitivity of chemical shift MRI. Additionally, some metastases and adrenocortical carcinomas have ratios in the adenoma range [47]. The overall sensitivity for detection of adenomas is 78% to 82% with a specificity of at least 87% [15,48].

**Nuclear Scintigraphy**

Adrenocortical scintigraphy provides images of uptake of radioactive cholesterol analogs. Scanning utilizes NP59, an I-131 labeled cholesterol analog that is available from the University of Michigan as an investigational new drug [49,50]. In Europe, an alternative agent is selenium-75, selenomethylcholesterol. False-negative scans are common for masses smaller than 2 cm in diameter [51].

Unlike nuclear scanning for thyroid nodules, the vast majority of apparently “nonfunctioning” adrenal adenomas are “hot.” Uptake on the same side (“concordant with”) the mass on CT was reported in 93% of clinically silent cortical adenomas [49]. Discordant uptake is generally found for metastatic lesions, nonfunctional adrenocortical carcinoma, cysts, and other space-occupying lesions. Rarely, discordant uptake has been reported in metastatic cancer (eg, renal cell carcinoma) [52]. Scanning can be useful for masses that are appear to be lipid-containing by MRI or have borderline CT “washout” results but otherwise do not have imaging characteristics (eg, irregular borders) that compel removal. In this setting, a discordant uptake on scintigraphy would suggest the mass is an adrenocortical adenoma whereas a discordant uptake would suggest it is an adrenocortical carcinoma.

Rare “collision” tumors may cause incorrect interpretations [53]. A collision tumor represents 2 adjacent tumors, such as an adrenal adenoma and a metastatic lesion. In this circumstance, the nuclear scan may reflect 1 tumor, but not the adjacent tumor. Careful review of the CT scan should permit proper assessment.

**PET**

PET using 18-fluorodeoxyglucose detects metastatic lesions in the adrenal. Standardized uptake values (SUV) are calculated for the lesion. In 1 study, the SUV for metastases ranged from 2.3 to 26.1, while benign lesions had SUV between 0.5 and 3.3 [54]. Reported SUV for benign lesions has ranged up to 4.8 [55]. While there is overlap, sensitivity for detection of malignancy has been greater than 93% with specificity greater than 94% [56]. Incorporating CT information can sometimes permit identification of adenomas where PET suggested a malignant lesion [54].

**What are the implications of mass size?**

Mass size is associated with risk of adrenocortical carcinoma. Adrenal adenomas 6 cm or larger in diameter are rare, with 3 found among 12,000 autopsies. In clinical series, adrenocortical carcinomas represent approximately 25% of masses greater than 6 cm; only approximately 18% of these large masses are adenomas [57].

Masses smaller than 6 cm, however, should not be ignored. Incidentally discovered adrenocortical carcinomas smaller than 2 cm have been reported [58]. In addition, the CT scan can underestimate the diameter of an adrenal mass by as much as 30%. Adrenal tumors are often elliptical, and transverse slices underestimate the superior-inferior dimension. A tumor that is actually 6 cm may be estimated as small as 4.2 cm on the CT scan. Some of these measurement difficulties may be avoided if 3 orthogonal dimensions are recorded from the volumetric data available with current multidetector row CT scanners [11].

**What is the role of fine-needle aspiration?**

Fine-needle aspiration (FNA) of the adrenal may be done under CT or ultrasound guidance [59–63]. Minor complications (eg, pain) are reported in 10% to 15% of patients. Major complications, such as hemorrhage, pneumothorax, or abscess occur in less than 13%. Needle track seeding by metastases has been reported [64]. Phaeochromocytoma should be excluded prior to FNA to avoid precipitating a crisis.

The major role of FNA is diagnosing malignancies metastatic to the adrenal gland. If CT or MRI studies are equivocal and a distinction of adenoma from metastasis is required for treatment planning, a FNA has excellent yield. In 4 large series, FNA was diagnostic in 221 of 254 biopsies [59–62].

FNA is not generally useful in distinguishing adrenocortical adenoma from adrenocortical carcinoma. Only an exceptional carcinoma may be identified by extreme atypia, such as cellular pleomorphism, variably shaped nuclei in a multinucleated cell, and numerous atypical mitoses [65]. Future work may employ gene expression. Notably, insulin-like growth factor II overexpression has been frequently observed
ADRENAL INCIDENTALOMAS

in pathology specimens from adrenocortical carcinoma but not from adenomas [66].

Workup and Assessment

The patient has several symptoms of Cushing’s syndrome with abdominally localized weight gain, round face, edema, muscle weakness, fatigue, and worsened hypertension. An overnight 1-mg dexamethasone suppression test yields a serum cortisol of 3.8 μg/dL. A 24-hour urinary free cortisol is slightly elevated at 47 μg/dL (normal, 4–45 μg/dL). One midnight salivary cortisol is elevated at 0.27 μg/mL (normal, up to 0.18 μg/mL for females aged 31–50 years), although another is top-normal at 0.17 μg/mL. A random serum cortisol is 10.2 μg/dL and an ACTH is 6 pg/mL. Serum aldosterone, plasma renin activity, plasma metanephrine and normetanephrine, and 24-hour urinary fractionated metanephrines and catecholamines are normal.

Since the patient has symptoms attributable to cortisol excess and biochemical evidence of cortisol hypersecretion, she is offered an adrenalectomy.

• What procedure should be used for resection of an adrenal mass?
• What tests are indicated prior to surgery?

The options for surgical removal of an adrenal mass include open (transabdominal and posterior) and laparoscopic (transperitoneal and retroperitoneal) procedures. Until recently, larger masses were exclusively removed by open procedures. Laparoscopic adrenalectomy has been successful with large tumors provided there is no evidence of extra-adrenal or vascular invasion [67,68]. Laparoscopy has also been used for removal of an isolated metastatic mass in patients with favorable prognostic features such as long disease-free interval [69,70]. Selective removal of the tumor, sparing the adjacent normal adrenal gland, has been used for benign tumors [71,72]. CT-guided radiofrequency ablation has also been used for removal of an isolated metastatic mass in patients with favorable prognostic features such as long disease-free interval [69,70]. For all procedures, patients with evidence for hypercortisolism should be protected from adrenal insufficiency with perioperative corticosteroid supplementation.

Positive hormonal screening should be confirmed prior to surgery. Generally, there should be at least 2 abnormal tests of cortisol hypersecretion combined with clinical features of cortisol excess prior to removal of a presumed cortisol-secreting adenoma [74]. Aldosteronomas should be confirmed by a suppression test. In patients older than 40 years, where nonfunctioning adenomas are more common, a selective adrenal vein catheterization study should be done to confirm the incidentaloma as the source of the excess aldosterone [75,76]. If the diagnosis of pheochromocytoma is uncertain, a clonidine suppression test can be performed [77]. If the CT scan is not suggestive of pheochromocytoma, a nonadrenal pheochromocytoma concurrent with a nonfunctioning adrenal adenoma should be considered [78]. Additionally, several authors recommend a metaiodobenzylguanidine (MIBG) scan prior to surgery to exclude metastatic pheochromocytoma [79].

Follow-up

The patient undergoes a transperitoneal laparoscopic left adrenalectomy. Pathology shows an adrenocortical adenoma. She takes prednisone 5 mg daily postoperatively and eventually is fully weaned off at 6 months after surgery. At 1 year after surgery, she no longer needs olmesartan or hydrochlorothiazide to control her blood pressure and no longer requires potassium supplements. She continues sustained-release metoprolol for her episodes of tachycardia. Her weight remains the same, but her headaches clear, her peripheral edema resolves, and she no longer feels tired.

• What changes can be expected after removal of an adrenal adenoma in a patient with subclinical Cushing’s syndrome?

Glucose tolerance, hypertension, and obesity have been noted to improve following resection of adenomas associated with subclinical Cushing’s syndrome [30]. Bone density improvement has yet to be convincingly demonstrated; it remains controversial whether subclinical Cushing’s syndrome causes bone mineral loss [57,80].

Follow-up in patients who do not undergo surgery has 2 main concerns: possible evolution of hormonal excess and identification of a malignancy missed on the original evaluation. Progression to hormonal hypersecretion has been said to occur in up to 20%, but a large careful study found fewer than 2% progressed over 3 years [2]. The risk for progression of cortisol hypersecretion is greater among masses larger than 3 cm. In one series, 1 of 8 patients with subclinical Cushing’s syndrome subsequently manifested full Cushing’s syndrome [81]. Pheochromocytoma first detected at follow-up has been reported rarely [82].

It has been recommended that patients be re-evaluated
annually for 4 years for cortisol excess (by a 1-ng overnight dexamethasone suppression test) and for pheochromocytoma (by a 24-hour urine for catecholamines and metabolites) [24]. Since progression to hypercortisolism is rare with tumors less than 3 cm, among patients with smaller tumors it may be reasonable to reserve repeat dexamethasone suppression testing for those with manifestations of glucocorticoid excess (eg, weight gain, hypertension, glucose intolerance, low bone density). Follow-up evaluation with urinary fractionated metanephrines is reasonable for patients whose masses had imaging characteristics compatible with pheochromocytoma.

Repeat CT scan at 6 to 12 months has been recommended [24]. There have been rare reports of adrenocortical carcinoma apparently arising from an adenoma, but malignant transformation is decidedly exceptional [83]. Overwhelmingly, benign tumors tend to maintain their benign nature. Therefore, if the tumor can be confidently classified as a cortical adenoma, several authors recommend no further imaging follow-up [84].

Additionally, however, masses originally misclassified as benign that prove to be carcinoma may grow slowly. Therefore, masses of a more indeterminate nature that are not immediately resected should be followed for enlargement at intervals up to 18 months (eg, at 3, 6, and 18 months). It should be borne in mind that mass enlargement of more than 1 cm over 1 year, while disconcerting and likely to prompt resection, is not immediately malignant [23].

Masses that enlarge at a rate of more than 1 cm per year, while disconcerting and likely to prompt resection, are more likely to be malignant tumors [85]. In one series, all 4 tumors removed because of this criterion were benign [86].

SUMMARY

The majority of incidentally discovered adrenal masses are benign, nonfunctional adenomas. It is crucial to determine which masses represent functional adrenal tumors or malignancies. Imaging characteristics and endocrine testing provide guidance in these distinctions. Follow-up is necessary to exclude evolving endocrine function and to detect malignancy among those masses that are not conclusively benign at the initial evaluation.

Corresponding author: Paul M. Copeland, MD, 496 Lynnfield St., Lynn, MA 01904, pcopeland@partners.org.

References


CME EVALUATION: Approach to Incidentally Discovered Adrenal Masses

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Most incidentally discovered adrenal masses are
   (A) Adrenal cysts
   (B) Nonfunctioning adrenal adenomas
   (C) Cortisol-producing adenomas
   (D) Metastases

2. Which of following statements about pheochromocytoma is FALSE?
   (A) It accounts for approximately 10% of adrenal incidentalomas
   (B) A homogenous mass < 2 Hounsfield units on unenhanced computed tomography (CT) scan is incompatible with the diagnosis
   (C) It is common in patients with a history of hypertension or paroxysmal symptoms
   (D) The condition must be excluded prior to fine-needle aspiration of the adrenal gland

3. Which of the following tests is used to screen for cortisol hypersecretion?
   (A) 1-mg overnight dexamethasone suppression test
   (B) 24-hour urinary catecholamines
   (C) Fractionated metanephrines
   (D) None of the above

4. Which of the following statements about adrenocortical carcinoma (ACC) is TRUE?
   (A) ACC commonly arises from an adenoma
   (B) ACC accounts for approximately 5% of incidentalomas
   (C) Fine-needle aspiration can help distinguish ACC from adenoma
   (D) None of the above

5. A patient is found to have a nonfunctioning heterogenous mass on unenhanced CT that is 7 cm in diameter. What is the appropriate next step?
   (A) Surgical removal
   (B) Evaluate for cortisol excess
   (C) CT washout
   (D) Positron emission tomography
   (E) None of the above
EVALUATION FORM: Approach to Incidentally Discovered Adrenal Masses

Participants may earn 1 credit by reading the article named above and correctly answering at least 70% of the accompanying test questions. A certificate of credit and the correct answers will be mailed within 6 weeks of receipt of this page to those who successfully complete the test.

Circle your answer to the CME questions below:

1. A  B  C  D
2. A  B  C  D
3. A  B  C  D
4. A  B  C  D
5. A  B  C  D  E

Please answer the following questions:

1. How would you rate this educational activity overall?
   _ Excellent  _ Good  _ Fair  _ Poor

2. This article was fair, balanced, free of commercial bias, and fully supported by scientific evidence.
   _ Yes  _ No

3. Please rate the clarity of the material presented in the article.
   _ Very clear  _ Somewhat clear  _ Not at all clear

4. How helpful to your clinical practice was this article?
   _ Very helpful  _ Somewhat helpful  _ Not at all helpful

Please print clearly:

Name: ________________________________
MD/DO/Other: ________________________
Address: ________________________________________________
_________________________________________________________________
City: ______________________________________  Zip: __________
State: ____________________  Zip: __________
Phone: ________________________________
Fax: ____________________________________
E-mail: __________________________________

Are you a health care professional licensed to practice in the US/Canada who can use Category 1 AMA PRA CME credit to fulfill educational requirements?  ____ Yes  ____ No

Physicians are required to report the actual amount of time spent on the activity, up to the maximum designated 1 hour. The actual time spent reading this article and completing the test was ____________________.

Please mail or fax this sheet to:
Wayne State University, Division of CME
101 E. Alexandrine, Lower Level
Detroit, MI 48201
FAX: 313-577-7554

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Wayne State University School of Medicine and the Journal of Clinical Outcomes Management. Wayne State University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Wayne State University School of Medicine designates this educational activity for a maximum of 1 AMA PRA Category 1 credits. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Release date: 15 January 2007
Expiration date: 30 January 2008