A Diagnostic Approach for Evaluating the Adrenal Mass

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Cover Illustration by Christine Schaar
INTRODUCTION

An adrenal mass can be found as part of an evaluation for a specific complaint related to adrenal pathology or as an incidental finding on a radiographic investigation for unrelated issues (the adrenal incidentaloma). Most adrenal masses are either adrenal adenomas or malignant metastases. Other important adrenal tumors include adrenal carcinoma and pheochromocytoma. Postmortem studies performed prior to the advent of routine computed tomography (CT) reported prevalences of 1% to 6% for adrenal masses. As the use of CT and magnetic resonance imaging (MRI) for the evaluation of abdominal complaints became routine, the incidence of discovering adrenal masses premortem rose (to a range of 0.4%–4.4%), approaching the absolute incidence reflected by the postmortem data.

The work-up of an adrenal mass begins with a thorough history and physical examination and, importantly, a directed hormonal evaluation. Radiographic studies are then implemented to investigate positive or equivocal laboratory findings as part of the diagnostic schema. Knowledge of the prevalence of adrenal diseases is important in the evaluation of an adrenal mass.

ADRENAL INCIDENTALOMA

The widespread use of high-resolution radiographic techniques has led to the increasingly frequent detection of asymptomatic adrenal masses (adrenal incidentalomas). Common to all incidental findings are the difficulties encountered in trying to determine clinical significance and defining the optimal diagnostic approach in a cost-effective manner. The primary considerations in diagnosis are whether the lesion discovered is benign or malignant and whether it is functional or nonfunctional.

CASE PRESENTATION

Initial Presentation

A 50-year-old man is referred by his primary care physician to an endocrinologist for evaluation of a right adrenal mass discovered as part of a work-up for non-specific abdominal pain.

History

In the initial evaluation by his primary care physician, the patient complained of epigastric discomfort and excessive belching 2 hours after meals. On questioning he denied experiencing sleep disturbances, weight gain or loss, headaches, nocturia, polyuria, visual disturbances, a history of paroxysmal spells, easy bruising, or tremors. He has no significant past medical history and takes no medications. His sister has hypothyroidism, and his mother developed hypertension at age 65 years. He does not use tobacco. He has a glass of wine with dinner each night.

Physical Examination

Physical examination revealed a height of 6 ft and a weight of 192 lb. His blood pressure was 128/86 mm Hg and his heart rate was 72 bpm. His examination was notable for the absence of facial plethora or fat pad redistribution. Also absent were striae, ecchymoses, abdominal masses, tremor, and proximal muscle weakness.

Laboratory Evaluation

Serum laboratory evaluation revealed the following values: potassium, 4.2 mg/dL; sodium, 140 mg/dL; creatinine, 0.9 mg/dL; calcium, 9.0 mg/dL; and albumin, 4.0 mg/dL.

Results of a 24-hour urine collection evaluation were as follows: epinephrine, 10 µg/24 h (normal, 2–24 µg/24 h); metanephrine, 101 µg/24 h (normal, 90–690 µg/24 h); and cortisol, 21 µg/24 h (normal, 2–20 µg/24 h).

An overnight dexamethasone suppression test (1 mg) revealed a serum cortisol level of 1.1 µg/dL.
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Radiographic Evaluation

CT of the abdomen with oral contrast reveals a 3-cm homogeneous rounded right adrenal mass. The left adrenal gland is normal in size and appearance. Multiple gallstones are visualized. The case patient is referred to the endocrinologist for evaluation of the adrenal mass.

• What is the differential diagnosis for an incidentally discovered unilateral adrenal mass?

This case represents a common presentation for the incidentally discovered adrenal mass. An example of a CT scan of an incidentally discovered adrenal mass is shown in Figure 1. As is true with incidentally discovered masses elsewhere in the body, the majority are benign. However, the mass may represent a variety of pathologic conditions (Table 1) and thereby necessitates careful evaluation. This patient’s symptoms and the results of detailed questioning do not point to obvious adrenal pathology, although further investigation is still warranted.

• How should this patient’s mass be evaluated?

**DIAGNOSTIC APPROACH**

Several guidelines and algorithms have been suggested to address the evaluation of the adrenal incidentaloma. All logical approaches should evaluate for the presence of malignancy and hormonal function.

**Evaluation for Malignancy**

Malignant adrenal tumors either arise as primary adrenal carcinomas or, more commonly, as metastatic lesions to the adrenal gland. The prevalence is influenced by the patient population studied, with metastases to the adrenal gland responsible for up to 62% of incidental adrenal masses in some oncologic studies. Even in the absence of known cancer, the chance that an adrenal incidentaloma is a metastatic lesion is 25% to 35%. The most common tumors that metastasize to adrenal tissue are breast, lung, and colon. The case patient reports no worrisome signs or symptoms of obvious or occult malignancy.

In further weighing the possibility of malignancy, size is the most important predictor of risk of primary adrenal carcinoma. The risk of adrenal carcinoma increases significantly in masses greater than 6 cm. In one large series of adrenal tumors, 90% of all adrenal carcinomas were greater than 6 cm in diameter, but a small number of malignant tumors were also seen in the 4- to 6-cm range. Based on these and other data it is now recommended that an adrenal mass greater than or equal to 4 cm be surgically removed if determined not to be a metastatic lesion. Several studies have suggested that the prevalence of adrenal nodules increases with age, suggesting that accumulated molecular derangements might be responsible for their pathogenesis. Thus, the risk for malignancy might be lower in older patients than in younger patients. Some authorities propose that an age-size cutoff value be employed to balance the risk of malignancy with the difficulties involved in lifelong follow-up.

Radiographic features other than size are helpful in assessing the risk of malignancy. Lipid density, as measured by Hounsfield units (HU) on CT, can be useful in diagnosing benign adenomas. One study demonstrated that an unenhanced value of less than 10 HU was 100%

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**Figure 1.** (Left) Abdominal computed tomographic (CT) scan showing normal appearance of right and left adrenal glands (arrows). (Right) Abdominal CT scan depicting an incidentally discovered right adrenal mass (arrow).
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Specific and 85% sensitive for benign adenomas. In addition, benign adenomas are characteristically smooth, round, and homogeneous, whereas adrenal carcinomas tend to have a heterogeneous appearance with areas of necrosis, calcification, and hemorrhage. Metastatic lesions tend to display thick irregular borders and enhancing rims, together with high HU measurements.

Radiographic techniques are continuing to improve and can offer diagnostic clues to guide the clinician’s decisions in the management of mid-range masses. Nevertheless, radiographic evaluation alone is not sufficient for diagnosing malignancy. For example, one study evaluated the ability of MRI to determine malignant versus benign adrenal masses. All malignant masses identified by MRI as suspicious for carcinoma were histologically cancer, but the false positive rate in the study was 67%.

Evaluation for Hypersecretion

The morbidity associated with hormonal hypersecretion from adrenal masses is well known. Hypercortisolism can cause osteoporosis, hypertension, obesity, insulin resistance, and diabetes. Hyperaldosteronism can cause hypertension and hypokalemia. Excessive catecholamines cause hypertension and possibly a life-threatening hypertensive crisis. Excess androgens and estrogens contribute to hirsutism, hypogonadism, infertility, and fetal development abnormalities.

Hormonal screening in patients with an adenoma should be carried out in a cost-effective manner based on pretest probability in combination with knowledge of disease prevalence. Not every adrenal hormone should be evaluated in every patient. Because of the relatively high incidence of incidentalomas secreting cortisol (5%–14%) or catecholamines (3%–10%) it is generally accepted that all adrenal incidentalomas be screened for the presence of hypersecretion of these two hormones.

Pheochromocytoma is ruled out with plasma or 24-hour urine measurements of metanephrines and catecholamines. A detailed evaluation for pheochromocytoma is discussed later in this manual.

Evaluation of cortisol secretion with an overnight 1-mg dexamethasone suppression test and/or 24-hour collection of urinary free cortisol is used to exclude Cushing’s syndrome. However, difficulties may arise in interpreting cortisol measurements for two important reasons. First, a variety of conditions exist—such as obesity, depression, and alcohol use—which can influence both static and dynamic testing of cortisol secretion leading to a significant false-positive rate. Second, mildly elevated serum or urine cortisol, or “subclinical” hypercortisolism, is present in 5% to 14% of incidentalomas. Low adrenocorticotropic hormone (ACTH) levels have been reported in about 5% to 34% of patients with adrenal incidentalomas. Initially, it was not known what long-term clinical significance this mild cortisol excess represented. However, it now appears that subclinical hypercortisolism has significant morbidity. One study reported high rates of obesity (50%), hypertension (92%), hypercholesterolemia (50%), and glucose intolerance or diabetes mellitus (58%) in patients with adrenal incidentalomas and “subclinical” Cushing’s syndrome based on 24-hour urine cortisol measurements.

In the setting of equivocal test results for the presence of hormone secretion, some studies have investigated the use of scintigraphy with radiolabeled cholesterol derivatives to demonstrate hyperfunctioning lesions. These studies have reported mixed results. Because this testing uses a radiolabeled steroid, the presence of adrenal “uptake” does not imply that an end product with functional significance is being produced.

The clinical history and examination of the patient with an incidentaloma should dictate the need for further hormonal testing. Hyperaldosteronism is rare, but when hypertension and/or unexplained hypokalemia are present, then measuring plasma renin activity and aldosterone activity will facilitate the work-up. An elevated aldosterone-to-plasma renin activity ratio (> 30) suggests the diagnosis of primary hyperaldosteronism. When the baseline renin is less than 0.5 ng/mL per hour, the value should be set at 0.5 to avoid a multiplier effect.

### Table 1. Differential Diagnosis and Frequency of Incidentally Discovered Adrenal Masses

<table>
<thead>
<tr>
<th>Type of Mass</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>51</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>31</td>
</tr>
<tr>
<td>Cyst</td>
<td>4</td>
</tr>
<tr>
<td>Adrenal cancer</td>
<td>4</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>4</td>
</tr>
<tr>
<td>Lipoma</td>
<td>2</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>2</td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>2</td>
</tr>
<tr>
<td>Other masses*</td>
<td>Rare</td>
</tr>
</tbody>
</table>

*Other masses include infection, ganglioneuroma, lymphoma, granuloma, and hemangioma.

of lower renin levels. Also, aldosterone levels greater than 15 ng/mL make a high ratio more sensitive.

If signs or symptoms of virilization or feminization are present, indicators of serum androgens (eg, dehydroepiandrosterone sulfate [DHEA-S], testosterone, urine 17-ketosteroid excretion), and estradiol should be measured. Because androgen excess is more frequent in adrenal carcinoma, some authors have suggested that DHEA-S and/or 17-ketosteroids should be measured when larger masses are present.17

**Further Evaluation**

When it is determined by hormonal evaluation that a mass is not functional and by radiographic evaluation that its size is less than 4 cm, the next step may be to determine whether it represents metastatic cancer from a nonadrenal source. Percutaneous biopsy by fine needle aspiration (FNA) with CT guidance, by an experienced clinician, is the preferred method for sampling adrenal masses. Studies have demonstrated the safety, accuracy, and reliability of this method for determining the content of masses of nonadrenal origin. The role of FNA in evaluating primary adrenal cortical malignancy, however, has been limited to ruling out disease—a negative FNA biopsy result cannot exclude a primary malignancy. However, recent studies have shown 93% sensitivity and negative predictive values of 91% for ruling out adrenal cancer when an adequate diagnostic specimen is obtained.18 FNA should not be performed unless pheochromocytoma is excluded to avoid precipitating a life-threatening hypertensive crisis from catecholamine release.

A diagnostic algorithm for approaching an incidentally discovered adrenal mass is shown in Figure 2.

**FOLLOW-UP OF NONFUNCTIONAL, APPARENTLY BENIGN ADRENA L MASSES**

Patients with nonfunctioning, apparently benign adrenal masses should be followed radiographically to look for changes in tumor size (increase ≥ 1 cm) and appearance, and biochemically to monitor the development of hormonal hypersecretion. Some centers may not have access to FNA evaluation, in which case repeat clinical evaluation with radiographic and biochemical follow-up are of great importance.

The recommended interval and method of follow-up of these tumors varies, but generally, an imaging study should be performed every 3 to 6 months for the first year and then yearly for the next 3 to 4 years. Large masses should be screened at shorter intervals than small masses. The value of repetitive screening for biochemical hyperfunction is debated, but because some functional tumors secrete episodically, most authorities recommend at least one additional hormonal evaluation.

The risk of malignant transformation appears remote. In one study that followed 75 patients for a mean of 2.5 years (median = 4.5 years) with adrenal incidentalomas that were less than 4 cm in size and were felt to be nonfunctioning and benign, no cases of malignancy were found.19 In this study, biochemical and radiographic studies were performed yearly. Nine masses (12%) increased in size, 3 masses (4%) developed cortisol hypersecretion, 3 masses (4%) showed both an increase in size and an increase in cortisol production,
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An adrenal incidentaloma is an asymptomatic adrenal mass discovered incidentally during imaging for another purpose. The incidence of adrenal incidentalomas is approximately 1% to 6% in the general population, and their prevalence increases with age. The reported range of adrenal hyperfunction in incidentalomas is 10% to 16%, and that of mass enlargement is 0% to 11%, with follow-up terms ranging from 3 months to 12 years. Overall, the vast majority of cases, adrenal incidentalomas initially determined to be benign and nonfunctioning remain so.

CASE RESOLUTION

FNA of the case patient’s incidentaloma reveals normal-appearing adrenal cortical cells. The patient undergoes elective laparoscopic removal of his gallbladder resulting in resolution of his abdominal complaints. Six months later, however, a follow-up CT study of the adrenal mass reveals an increase in size to 5 cm. Results of a repeated hormonal evaluation are again normal. He undergoes surgical removal of the mass without complications. The final pathologic report demonstrates a benign adrenal tumor.

ADRENAL CARCINOMA

Adrenal carcinoma is an extremely rare but highly aggressive malignancy. Survival is typically measured in months from diagnosis. Treatment is often limited because the tumor is usually at an advanced stage at the time of diagnosis. Symptoms at presentation vary depending on the functionality of the tumor and its size. Treatment consists of adrenolytics and surgical debulking to control symptoms and, more recently, combination chemotherapy to improve survival. Adrenal carcinoma is shown in Figure 3.

CASE PRESENTATION

Initial Presentation

A 68-year-old woman is referred to an endocrinologist for complaints of increasing fatigue, easy bruising, frontal-temporal hair loss, coarsening of facial features, and hirsutism.

History

The patient reports that these symptoms began about 6 months ago when she noted difficulty climbing stairs and an inability to maintain her daily running schedule. Over the ensuing months, she noted facial fullness, swelling of her ankles, and easy bruising, and recently suffered an atraumatic wrist fracture. Upon returning from a semester at college, her daughter noted a drastic change in her mother’s facial features that included new coarse facial hair growth and temporal-parietal balding. The patient’s past medical history is notable for menopause at age 52, an active healthy lifestyle, and no known prior medical problems. Family history is significant for hypertension in her father, but there is no family history of endocrinopathies or cancer.

Physical Examination

Physical examination reveals an ill-appearing, fatigued woman whose height is 5’4” and weight is 146 lb. Her pulse is 98 bpm, blood pressure is 152/96 mm Hg, and respiratory rate is 18 breaths/min. Her facial features are coarsened. She has excess terminal hair growth over the face, chest, and abdomen; male pattern balding; centripetal obesity; numerous ecchymoses; and ankle edema. Most notable is the presence of a large, nontender, irregular mass palpated in the upper abdominal quadrants. A driver’s license photograph reveals striking changes in her appearance from 2 years ago.
Laboratory and Imaging Evaluation

Results of laboratory testing are as follows:

- Serum potassium, 3.9 mg/dL
- Serum glucose (fasting), 145 mg/dL
- Serum creatinine, 1.2 mg/dL
- Leukocyte count, 19.0 × 10^3/mm^3; differential, 89% polymorphonuclear cells
- Total testosterone, 1900 pg/mL (normal, 80–830 pg/mL)
- DHEA-S, 5.2 pg/mL (normal, 0.4–3.2 pg/mL)

Results of a 24-hour urine collection are as follows:

17-ketosteroids, 134 mg/24 h (normal, 4–18 mg/24 h); cortisol, 260 µg/24 h (normal, 2.0–42.4 µg/24 h); and metanephrines, 102 µg/24 h (normal, 95–475 µg/24 h).

A lateral chest radiograph demonstrates a compression fracture at the tenth thoracic vertebra. Abdominal CT reveals a 14-cm mass with irregular borders arising from the right adrenal gland extending into the liver. Areas of necrosis, hemorrhage, and calcification are present.

Based on this patient’s clinical presentation, physical exam, and laboratory and imaging findings, what is the most likely diagnosis?

This unfortunate woman demonstrates the classic history, physical examination findings, laboratory profile, and radiographic features of adrenal carcinoma.

EPIDEMIOLOGY

Adrenal carcinoma is a rare cancer that can develop at any age and equally in both sexes. The estimated incidence in the United States is 0.1 to 2.0 cases per million persons per year, and it represents 0.2% of all cancer deaths per year. There is no influence of race on incidence. The mean age at diagnosis is distributed bimodally, with peaks in the first and fourth decades. The mean age at diagnosis appears to predict prognosis only when children (more favorable prognosis) are compared to adults.

The mean duration from onset of symptoms to the time of diagnosis ranges from 6 to 16 months and is not influenced by whether the tumor secretes excess hormone.

CHARACTERISTICS OF ADRENAL CARCINOMA

Functional adrenal carcinomas may secrete more than one hormone, as in this patient’s case. Case series reporting steroid profiles plotted by level or type resemble a scattergram with a variety of hormones and hormone precursors displayed in a range of concentrations characteristic of inefficient steroid synthesis. Hypersecretion associated with adrenal carcinomas may result in Cushing’s syndrome, feminizing or virilizing syndromes, or a mix of Cushing’s syndrome with either feminizing or virilizing features. Rarely, tumors secrete excess insulin-like growth factor II, antidiuretic hormone, and/or mineralocorticoid hormones. Tumors that do not secrete hormones at levels that are clinically evident are considered “nonfunctional” even though excessive steroid precursors might be detected biochemically. Many adrenal carcinomas, including nonfunctional tumors, present with abdominal pain, a palpable mass, and constitutional symptoms. Some tumors that initially appear nonfunctional may subsequently develop excess hormone secretion. However, the presence or absence of function has no effect on subsequent mortality.

Classic clinical features of adrenal carcinoma therefore depend on the amount and type of hormone synthesized. The most common hormonal abnormalities are cortisol excess and androgen excess (eg, from testosterone or androgen precursors such as DHEA-S). Signs of cortisol excess include hypertension, edema, ecchymoses, fat pad redistribution, glucose intolerance, and osteoporosis. Signs of virilization from androgen excess include male-pattern hair loss and excess body hair distribution on the chest, abdomen, and upper back. Feminizing tumors in males from excess of estrogen present with gynecomastia and testicular atrophy. Children with adrenal carcinomas more frequently have virilizing findings, whereas adults tend to display mixed findings.

HORMONAL AND RADIOGRAPHIC EVALUATION

Because adrenal carcinomas can secrete a myriad of clinically significant hormones and hormone precursors, biochemical screening should be undertaken as in the evaluation of an adrenal incidentaloma. CT is the favored imaging procedure in evaluating adrenal malignancy. CT may also help determine the presence of metastases and/or the extent of local invasion as it relates to possible surgical evaluation and cancer staging.
PROGNOSIS AND TREATMENT OPTIONS

Adrenal carcinomas are highly malignant cancers with 50% to 70% of them exhibiting locally advanced disease at the time of presentation. The prognosis for untreated patients is dismal, with a mean life expectancy of 2.5 months. A staging system was designed to categorize the extent of disease but has little impact on outcomes. Five-year survival rates in very aggressively treated patients range from 30% to 60%.

Surgical resection is only rarely curative in early-stage adrenal carcinomas, and its role as a cure is controversial in most settings. The majority of patients experience recurrence owing to presumed micrometastases, making the role of surgery more palliative. Surgery may be employed to debulk tumor burden and diminish symptoms of hormonal excess.

Chemotherapeutic agents targeted against adrenal carcinomas have also failed to provide cure in most studies but have been shown to both prolong life and improve quality of life. Mitotane is an adrenocorticalytic drug that may have some activity when used as primary treatment, although results are variable and often contradictory. Mitotane is sometimes used as adjuvant treatment with surgery in selected patients, again with varying results. Its efficacy is difficult to ascertain because of poor patient tolerance owing to its frequent gastrointestinal side effects (nausea, vomiting, anorexia, and diarrhea). Because it is adrenocorticalytic, patients are often started on simultaneous prednisone replacement therapy to avoid adrenal insufficiency. Other possible regimens combine mitotane with chemotherapeutic agents such as etoposide, doxorubicin, cisplatin, or cyclophosphamide. Experimental agents, including gossypol and suramin, also exist for patients whose tumor progresses despite therapy with mitotane.

CASE RESOLUTION

Based on the patient’s extensive disease, she was scheduled for surgical debulking. At the time of surgery, a 14- by 14.5- by 8-cm adrenal mass was isolated and removed. Multiple hepatic nodules were noted. Final pathologic examination of both the mass and the hepatic nodules revealed adrenocortical carcinoma. The patient was started immediately on low-dose mitotane therapy but shortly thereafter discontinued it because of intolerable gastrointestinal complaints. She died 4 months later.

PHEOCHROMOCYTOMA

Pheochromocytoma is a rare tumor of chromaffin cells that should be considered in the evaluation of patients with hypertension, arrhythmias, panic disorders, adrenal incidentalomas, and certain familial disorders. The prevalence depends on the population being studied but ranges from less than 0.1% to 0.3% in the hypertensive population and as high as 4% in patients with adrenal incidentalomas. Most cases of pheochromocytoma are sporadic, although familial predispositions are seen in a variety of disorders. The proper diagnosis and localization of pheochromocytoma is important, although frequently problematic; this rare disease can be cured in 90% of cases, but if left undiagnosed, can lead to significant morbidity and mortality.

CASE PRESENTATION

Initial Presentation

A 28-year-old man is referred to an endocrinologist for evaluation of new onset severe hypertension and an adrenal mass discovered during a recent hospitalization.

History

The patient met with his primary care physician because of episodic headaches and chest pounding with accompanying pallor, nausea, and sweating. In the physician’s office, he was noted to have new hypertension (blood pressure of 148/92 mm Hg). He had no significant medical history and took no medications. He denied drug, alcohol, or tobacco use and stated that he was very athletic. His father and paternal grandfather developed hypertension in their 40s. Laboratory studies returned normal values for serum electrolytes, kidney function, and urinalysis, and results of an electrocardiogram (ECG) were normal. He was prescribed atenolol 50 mg/day. During the following week his symptoms worsened, leading to a presentation at a local emergency department with symptoms of chest pressure, headache, and blurred vision. His blood pressure was 210/124 mm Hg. A head CT revealed no acute abnormalities. An ECG showed diffuse ischemia, and cardiac enzymes were mildly elevated. Serum electrolytes were normal, but serum creatinine was 2.2 mg/dL, and urinalysis revealed 2+ protein level. Serum and urine toxicology studies were negative. He was admitted to the medical intensive care unit and started on intravenous nitroprusside, resulting in gradual resolution of his severe hypertension and associated symptoms.

Physical Examination

In the endocrinologist’s office the patient is described as non-obese and well conditioned. Height is 6’3”, weight 210 lbs. Blood pressure is 148/90 mm Hg; heart rate is 90 bpm. Results of a funduscopic examination are normal, his thyroid is normal and neck bruits are absent, no cardiac murmurs or extra heart sounds are
detected, no abdominal masses are palpated or bruits auscultated, no extremity edema is present, and there is no tremor of the outstretched hands.

- What is the most likely cause of this patient’s symptoms?

**DIAGNOSIS OF PHEOCHROMOCYTOMA**

This man presents with signs and symptoms of adrenal pheochromocytoma. He reports paroxysmal “spells” of headaches, palpitations, visual disturbances, pallor, and sweating. He has a new and severe hypertension that worsens with unopposed β-blockade. The hallmark of symptomatic pheochromocytomas is the presence of paroxysmal signs and symptoms, present in about 60% of patients with this condition (Table 2).

Establishing the diagnosis of pheochromocytoma is important because even slight stimuli can incite discharge of catecholamines with possible fatal results. Importantly, surgical removal can cure 90% of patients.

- What further diagnostic testing should be performed in the evaluation of this patient?

**Biochemical Diagnosis**

Making the diagnosis of pheochromocytoma requires demonstration of excessive catecholamine secretion, determined by measurement of urine or plasma catecholamines or their metabolites (metanephrines and vanillylmandelic acid [VMA]). Ideally, sample collection should be made at the time of a “spell” for the greatest yield, although most patients have markedly elevated catecholamine secretion even in the absence of paroxysmal symptoms. Complicating the specificity of this evaluation are other conditions that can contribute to excess catecholamine production (Table 3); in addition, pheochromocytomas may occasionally have episodic secretion.

In deciding on a particular test to confidently diagnose or exclude pheochromocytoma, one must weigh the likelihood of a false-negative result. For this reason, most experts recommend measuring urine or plasma metanephrines because of their high sensitivity in ruling out pheochromocytoma. A positive biochemical screening test such as this will invariably result in more false positives than true positives. In patients with pheochromocytoma, levels of vanillylmandelic acid (VMA), catecholamines, or metanephrines from a 24-hour urine collection are typically more than 3 times higher than the laboratory reference range for normal. The meticulous review of alternative reasons for elevated catecholamines and/or metabolites and a careful clinical examination can help decrease this false-positive rate. In addition, serial measures can be employed to build confidence in the diagnosis. Plasma metanephrine testing has recently been reported to have the highest level of sensitivity (up to 99%) when compared to other hormonal measures. Pheochromocytomas tend to secrete metanephrines continuously, whereas catecholamines and metabolites are secreted episodically.

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**Table 2. Relative Frequency of Paroxysmal Symptoms in Patients with Pheochromocytoma**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency of Occurrence (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>82</td>
</tr>
<tr>
<td>Headache</td>
<td>58</td>
</tr>
<tr>
<td>Palpitations</td>
<td>48</td>
</tr>
<tr>
<td>Sweating</td>
<td>37</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Flushing/pallor</td>
<td>18</td>
</tr>
</tbody>
</table>


**Table 3. Causes of Sympathetic Overactivity Other Than Pheochromocytoma**

- Autonomic dysfunction
  - Spinal cord injury
  - Guillain-Barré syndrome

- Stress response
  - Postsurgical
  - Panic reaction

- Abrupt discontinuation of sympathetic antagonists
  - Propranolol
  - Clonidine

- Sympathomimetic drugs
  - Phenylpropanolamine
  - Cocaine
  - Amphetamine
  - Phenylephrine
  - Terbutaline
  - MAOI with tyramine

MAOI = monoamine oxidase inhibitor.
In some cases, the use of dynamic testing clarifies equivocal results. Clonidine suppression and glucagon stimulation tests are two methods for discerning other causes for catecholamine excess from pheochromocytoma. Both tests should only be performed by experienced clinicians because of the risk of hypotension or hypertension with the administration of clonidine or glucagon, respectively.

Localization of Tumor

The approach to diagnosing a pheochromocytoma begins first with biochemical evidence of catecholamine or catecholamine-metabolite excess. Imaging studies should not be performed to evaluate a patient with symptoms before establishing the diagnosis, because the information can be misleading given the relatively high rate of adrenal incidentalomas. Once biochemical evidence is established, the patient should be treated while further evaluation proceeds.

Approximately 10% of pheochromocytomas are found outside the adrenal gland, most often in the abdomen. Fewer than 2% occur outside the abdomen. Additionally, approximately 10% occur bilaterally and 10% are malignant. Extra-adrenal pheochromocytomas may be located in the superior and inferior para-aortic areas (75%); followed by the bladder (10%); thorax (10%); and head, neck, and pelvis (5%).

CT or MRI of the abdomen is the preferred initial radiographic technique. Both are sensitive (CT, 93%–98%; MRI, up to 100%) but they yield only 70% specificity because of the relatively high incidence of incidentalomas. CT involves the use of intravenous contrast and there is a slight risk of triggering a hypertensive crisis as a result of contrast administration. Pheochromocytomas show marked enhancement with contrast. MRI is more expensive but does not require the use of contrast dyes and has no radiation exposure. Pheochromocytomas on T2-weighted MRI images frequently appear hyperintense when compared to liver.

Metaiodobenzylguanidine (MIBG) scintigraphy may be used when the biochemical and clinical suspicion persists despite absence of CT or MRI evidence of pheochromocytoma or when attempting to locate multiple or extra-adrenal tumors. MIBG is a derivative of catecholamine precursors and is taken up by adrenergic tissue.

Finally, FNA of a suspected pheochromocytoma should be avoided to prevent potentially life-threatening hypertensive crisis from tumor stimulation.

CONTINUED PATIENT EVALUATION

Laboratory Evaluation and Imaging

Urine and plasma collections for metanephrines and catecholamines are obtained, revealing a plasma epinephrine level of 34,585 pg/mL (normal, 0–49 pg/mL supine) and a plasma norepinephrine level of 80,303 pg/mL (normal, 112–658 pg/mL supine).

Results of a urine 24-hour collection are as follows:

- Epinephrine, 1149 µg/24 h (normal, 2–24 µg/24 h)
- Norepinephrine, 1607 µg/24 h (normal, 15–100 µg/24 h)
- Metanephrine, 16,132 µg/24 h (normal, 90–690 µg/24 h)
- Vanillylmandelic acid, 45 mg/24 h (normal, 0–6 mg/24 h)

CT of the abdomen reveals a 3-cm right adrenal mass, homogeneous in appearance, with marked enhancement after intravenous contrast administration.

- How should this patient’s condition be managed?

TREATMENT

This patient’s labwork and imaging results support the diagnosis of pheochromocytoma. Patients with pheochromocytoma should be evaluated for surgical removal of the tumor. Preoperative management involves controlling blood pressure through the use of agents that block catecholamine receptors or action.

Agents that are effective in the treatment of pheochromocytoma act by either blocking catecholamine receptors or by interfering with catecholamine production. The most frequently used medication for treating the symptoms of pheochromocytoma is phenoxycbenzamine, an α-adrenergic receptor blocker. Other agents include prazosin, labetalol, and calcium-channel blockers. Pure β-adrenergic antagonists should be initially avoided because the consequent unopposed α-adrenergic stimulation can worsen hypertension, as evidenced in the present case. The inhibitor metyrosine may also have clinical benefits because it reduces tumor stores of active metabolites, acting at the rate limiting step of catecholamine synthesis by inhibiting tyrosine hydroxylase.

The high adrenergic tone in patients with pheochromocytoma frequently results in disturbances in volume/pressure homeostasis with a compensatory resetting of circulating volume to lower levels. In this volume-contracted state, patients often have orthostatic hypotension, particularly after starting medication. It is important to instruct patients to increase fluid and salt intake modestly to restore plasma volume in order to avoid symptomatic orthostatic hypotension.

The goal of pre-operative treatment is to adequately control blood pressure and thus reduce the likelihood...
of a hypertensive crisis, particularly intra-operatively. A typical treatment regimen for pheochromocytoma begins with 10 mg of phenoxybenzamine daily, raising the dose by 10 mg every 2 to 3 days until the time of surgery—10 to 14 days, at the earliest. Combination therapy with metyrosine and phenoxybenzamine might provide the most effective preoperative management to avoid large volume shifts.41 A β-blocker may be introduced if tachycardia is an issue after α-adrenergic blockade has been accomplished. Before the introduction of adrenergic blockade prior to surgery, surgical mortality was quite frequent (24% to 50%) in patients with pheochromocytoma.38 Presently, however, survival rates are 97.7% to 100% with proper presurgical treatment and close intraoperative hemodynamic monitoring.35

In the immediate postoperative period, diligent attention should be focused on avoiding hypotension by providing adequate fluid replacement. Surveillance for hypoglycemia should also be undertaken because hypoglycemia occurs in 10% to 15% of patients owing to the removal of catecholamine-induced insulin suppression.13

Malignant pheochromocytoma occurs in approximately 10% of cases.38 Malignancy is not easily determined by histopathologic examination; rather, it is revealed at the time of surgery based on the presence of metastasis or local invasion from the tumor.

FOLLOW-UP

Postoperative follow-up consists of the evaluation of plasma and/or urine metanephrine levels at approximately 6 weeks following surgery and again at 4 to 6 months to assure cure. Early postoperative assessment may show increased catecholamines for up to 2 weeks despite surgical cure. In familial forms of pheochromocytoma, recurrence rates tend to be high and annual surveillance is recommended.36 Again, biochemical results should dictate the need for any additional imaging studies.

Prognosis is very good, with 90% of patients cured with surgery. An observational study of 90 patients with pheochromocytomas revealed 20-year overall and cause-specific survival rates of 60% and 80%, respectively.42 Neither the rate of malignancy nor the survival curves for familial, sporadic, adrenal, or extra-adrenal forms were significantly different. This study describes a case of malignant transformation detected 15 years after diagnosis, signifying the need for long-term follow-up.42

Future research efforts will focus on developing more refined genetic markers to screen family members who are at risk of developing a pheochromocytoma, identifying markers of malignant potential, and developing cost-effective follow-up algorithms.14,15

CASE RESOLUTION

A MIBG scintiscan to exclude extraadrenal involvement of this patient’s pheochromocytoma demonstrated positive uptake in the corresponding adrenal mass only. The patient was started on 10 mg of phenoxybenzamine. His paroxysmal spells improved, but he was bothered by excessive thirst and lightheadedness. He was instructed to drink 2 liters of extra fluid per day and over the following week had less orthostatic hypotension. The phenoxybenzamine dose was increased to 40 mg/day in preparation for his adrenal surgery. He underwent right adrenalectomy 3 weeks later. Intraoperatively, he developed transient fluid-responsive hypotension upon removal of the adrenal gland. His postoperative course was uneventful. The final pathologist’s report described a 4.2 cm pheochromocytoma with clean margins and no sign of capsule or local invasion.

REFERENCES


