Pheochromocytoma
A Devious Opponent in a Game of Hide-and-Seek
Neelam H. Shah, MD; Daniel T. Ruan, MD

Case 1
M.G. is a 53-year-old woman with a history of episodic flushing, hypertension, and an incidentally discovered adrenal mass who presented with shortness of breath, weakness, and lightheadedness in the setting of hypertension to 300/200 mm Hg. Physical examination revealed an obese woman with a systolic ejection murmur and bibasilar crackles, but no neurological or ophthalmologic signs of hypertension. Plasma metanephrines were 0.50 nmol/L (normal: 0–0.49 nmol/L) and normetanephrines were 1.8 nmol/L (normal: 0–0.89 nmol/L); 24-hour urine epinephrine was 10 μg (normal: 0–20 μg) and norepinephrine was 119 μg (normal: 15–80 μg; Table). Autonomous hyperaldosteronism and hypercortisolism were excluded. Renal artery ultrasound was unremarkable; T2-weighted abdominal MRI revealed a 2.5 × 1.8 centimeter hypointense lesion in the right adrenal gland (Figure 1A). Presumed diagnosis was pheochromocytoma, for which appropriate preoperative preparation and surgery, as described later, were conducted.

Background
Pheochromocytoma, a catecholamine secreting mass located in the adrenal gland, is a rare but often fatal cause of hypertension. Annual incidence is 2 to 8 cases per million, but outpatient screening studies for secondary hypertension estimate a prevalence of 0.2% to 0.6%, primarily in the third through fifth decades, with no sex difference.1–10 Periodically-secreted catecholamines cause paroxysms of headache, flushing, palpitations, diaphoresis, anxiety, tremors, and severe hypertension that can rapidly lead to fatal stroke, arrhythmia, and myocardial infarction. Hypertension may be paroxysmal or persistent, and some patients may be normotensive as a result of hypovolemia, increased production of endogenous vasodilators, or downregulation of α-1 adrenergic receptors.1,11 The diagnosis is suspected in patients with episodic symptoms, a family history of the tumor, hypertension at a young age, idiopathic dilated cardiomyopathy, variable blood pressures, known suprarenal mass, adverse cardiovascular response to anesthesia, or refractory hypertension.11,12

Work-Up
The biochemical work-up of pheochromocytoma begins with the measurement of serum catecholamine metabolites (metanephrines and normetanephrines) and a 24-hour collection of urine catecholamines (epinephrine and norepinephrine), both of which are at least quadrupled in most patients with pheochromocytoma. Normal levels in a hypertensive symptomatic patient make the diagnosis unlikely but do not exclude it in a...
normotensive asymptomatic patient. Borderline results (<3-fold the upper limit of normal) warrant repeat measurement after 30 minutes of supine rest (Figure 2).

Elevated laboratory markers warrant anatomic imaging of the abdominal/pelvic region; patients with atypical presentations may require more extensive imaging (Figures 1 and 2). CT and MRI are equally sensitive in detecting pheochromocytoma, which is bright on T2-weighted MRI and vascular on contrast CT. For patients with equivocal imaging or a genetic predisposition for extra-adrenal or multifocal tumors, functional imaging such as 123I-MIBG (iodine-131-meta-iodobenzylguanidine) scintigraphy is appropriate.

When imaging is negative and medications or anxiety are the most likely cause of mild catecholamine elevation, clonidine suppression testing can sometimes exclude pheochromocytoma. Percutaneous biopsy may cause a dangerous surge of catecholamines and should not be used before definitive biochemical exclusion of pheochromocytoma.

**Treatment**

Definitive treatment is surgical removal after preoperative α- and β-blockade to prevent intraoperative crises. Preferred preparation is a 2-week course of phenoxybenzamine or doxazosin with progressive dosage escalation until the patient is orthostatic, but calcium channel blockers are also effective. A liberal salt diet and fluid boluses are used to counteract vasodilation-induced volume contraction and orthostatic symptoms. Intraoperatively, fluid boluses after isolation of the tumor are often necessary to treat α-blockade-induced hypotension. Sodium nitroprusside may be necessary for crisis-related hypertension, although lidocaine and beta blockers can be used to treat tachyarrhythmias.

When feasible, endoscopic adrenalectomy, using the laparoscopic or retroperitoneoscopic approaches, are preferred because they are associated with reduced mortality and length of stay. However, open adrenalectomy through a thoracoabdominal approach may be necessary for large or locally invasive tumors. Postoperatively, biochemical surveillance is recommended to screen for recurrent or persistent disease. Frequent screening CT or MRI scans are unnecessary if biochemical tests remain negative.

**Pheochromocytoma Imposters**

Pheochromocytoma is a potentially lethal cause of hypertension and important to rule out in a hypertensive patient. However, the condition is rare, and false positives on biochemical testing and imaging are common. In fact, 97% of hypertensive patients with elevated plasma fractionated metanephrines will not have pheochromocytoma, but may still receive imaging and potentially inappropriate surgery. Hence, it is necessary to exclude other causes of elevated catecholamine levels before initiating treatment (Figure 2).

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**Table. Serum and Plasma Catecholamine Metabolite Values**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>M.G.</th>
<th>J.C.</th>
<th>Pheochromocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma metanephrines</td>
<td>0–0.49 nmol/L</td>
<td>0.50 nmol/L</td>
<td>0.31 nmol/L</td>
<td>&gt;1.5 nmol/L</td>
</tr>
<tr>
<td>Plasma normetanephrines</td>
<td>0–0.89 nmol/L</td>
<td>1.8 nmol/L</td>
<td>11.7 nmol/L</td>
<td>&gt;2.7 nmol/L</td>
</tr>
<tr>
<td>24-hour urine epinephrine</td>
<td>0–20 µg</td>
<td>10 µg</td>
<td>18 µg</td>
<td>&gt;80 µg</td>
</tr>
<tr>
<td>24-hour urine norepinephrine</td>
<td>15–80 µg</td>
<td>119 µg</td>
<td>804 µg</td>
<td>&gt;240 µg</td>
</tr>
</tbody>
</table>

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**Figure 1. M.G. and J.C. Imaging. A, M.G: Abdominal MRI. B, J.C: Abdominal MRI.**
Incidentally discovered adrenal masses are also common, occurring in 4% to 6% in the general population, and as many as 70% of patients aged >70 years. Though most adrenal masses are benign, they cannot be ignored, as 10% to 15% of them may be malignant. Hence, although pheochromocytomas are benign in 4% to 6% in the general population, and as many as 70% of patients aged >70 years. Though most adrenal masses are benign, they cannot be ignored, as 10% to 15% of them may be malignant. Hence, although pheochromocytomas are benign, they cannot be ignored, as 10% to 15% of them may be malignant. Hence, although pheochromocytomas must be ruled out in a symptomatic and hypertensive patient with known adrenal mass, other causes of hypertension and adrenal mass, such as an aldosterone-secreting tumor, should also be considered.

Both M.G. and J.C. had adrenal incidentalomas. M.G. had many classic pheochromocytoma findings, including hypertensive emergency and flushing. In the setting of elevated urine and serum markers. Though her signs and symptoms were classic for pheochromocytoma, close evaluation of her biochemical studies and MRI hinted that she did not have a pheochromocytoma. Her plasma metanephrine level was only twice the upper limit of normal, and the mass was not particularly hyperintense on T2-weighted images. Ultimately, pathology confirmed her mass to be an adrenal adenoma, not a pheochromocytoma.

J.C.’s history, on the other hand, was negative for any classic pheochromocytoma symptoms, and she was hypertensive only during pregnancy, a time when hypertension is common. However, her biochemical markers were diagnostic of pheochromocytoma, with a serum normetanephrine and urine norepinephrine >10 times the upper limit of normal. The hyperintense mass on her MRI was also hyperintense on T2-weighted images. Ultimately, pathology confirmed her mass to be a pheochromocytoma.

Comparing these cases demonstrates not only how well pheochromocytoma can disguise itself, but also how well adrenal adenomas can mimic pheochromocytoma, particularly given the nonspecific symptoms often seen in perimenopausal women. The juxtaposition of these cases should serve as a call to have both a low threshold to consider pheochromocytoma as a potential diagnosis in a hypertensive patient and also a discerning mind to realize that not all seemingly classic stories will actually be pheochromocytoma.

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Disclosures
None.

References


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