Pheochromocytoma
A Devious Opponent in a Game of Hide-and-Seek
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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, 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.

Case 2
J.C. is a 30-year-old woman with a history of pregnancy-induced hypertension who presented with abdominal pain, vomiting, and bloody diarrhea. Physical examination was notable for normal vital signs and a mildly uncomfortable appearing woman with a systolic ejection murmur and diffusely tender abdomen. Plasma metanephrines were 0.31 nmol/L, and normetanephrines were 11.7 nmol/L; 24-hour urine epinephrine was 18 μg, and norepinephrine was 804 μg (Table). T2-weighted abdominal MRI revealed a 36-mm heterogeneous left adrenal mass (Figure 1B). Presumed diagnosis was pheochromocytoma, for which appropriate preoperative preparation and surgery 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.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 vasodilatation-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).
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. Alternative explanations can include medications (tricyclic antidepressants, minoxidil, hydralazine, labetalol, buspirone, acetaminophen), substance abuse (cocaine), anxiety, withdrawal (clonidine, alcohol), or medical problems (acute myocardial infarction/ischemia, New York Heart Association Class III or IV heart failure). Functional imaging: $^{123}$-MIBG scintigraphy. Extra-adrenal imaging: inferior para-aortic areas, bladder, thorax, head, neck, pelvis. Pheo indicates pheochromocytoma. 

Figure 2. Work-up of suspected pheochromocytoma. Algorithm only applies if there is diagnostic uncertainty with a strong plausible alternative diagnosis. If pheo is the leading diagnosis and delaying treatment could be harmful, imaging and surgery should not be delayed for further testing. Also note that pheo specifically refers to tumors that begin in the adrenal glands; extra-adrenal tumors with the characteristics described here are paragangliomas and not discussed here. Alternative explanations can include medications (tricyclic antidepressants, minoxidil, hydralazine, labetalol, buspirone, acetaminophen), substance abuse (cocaine), anxiety, withdrawal (clonidine, alcohol), or medical problems (acute myocardial infarction/ischemia, New York Heart Association Class III or IV heart failure). Functional imaging: $^{123}$-MIBG scintigraphy. Extra-adrenal imaging: inferior para-aortic areas, bladder, thorax, head, neck, pelvis. Pheo indicates pheochromocytoma.

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References


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