

> **THE PATIENT**
64-year-old woman

> **SIGNS & SYMPTOMS**

- Hot flashes, facial flushing, excessive sweating, and palpitations
- Daily headaches
- History of hypertension

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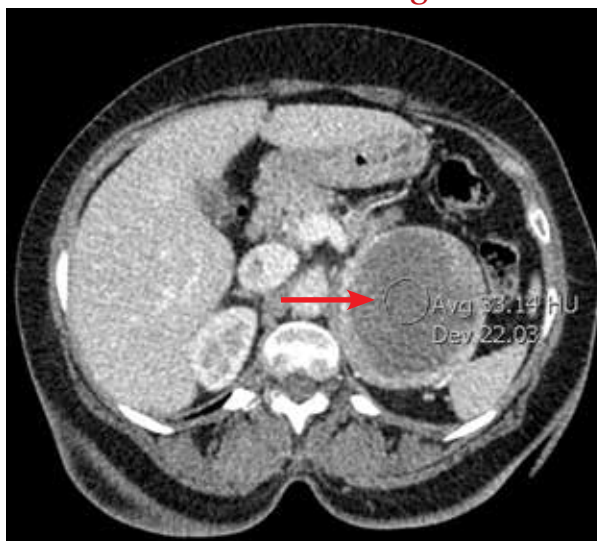
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> THE CASE

A 64-year-old woman sought care after having hot flashes, facial flushing, excessive sweating, palpitations, and daily headaches for 1 month. She had a history of hypertension that was well controlled with hydrochlorothiazide 25 mg/d but over the previous month, it had become more difficult to control. Her blood pressure remained elevated to 150/100 mm Hg despite the addition of lisinopril 40 mg/d and amlodipine 10 mg/d, indicating resistant hypertension. She had no family history of hypertension, diabetes, or obesity or any other pertinent medical or surgical history. Physical examination was negative for weight gain, stretch marks, or muscle weakness.

Laboratory tests revealed a normal serum aldosterone-renin ratio, renal function, and thyroid function; however, she had elevated levels of normetanephrine (2429 pg/mL; normal range, 0-145 pg/mL) and metanephrine (143 pg/mL; normal range, 0-62 pg/mL). Computed tomography (CT) revealed an 8.6-cm complex, hemorrhagic, necrotic left adrenal mass with attenuation of 33.1 Hounsfield units (HU) (FIGURE 1). Magnetic resonance imaging (MRI) demonstrated a T2 hyperintense left adrenal mass. An evaluation for Cushing syndrome was negative, and positron emission tomography (PET)/CT with gallium-68 dotatate was ordered. It showed intense radiotracer uptake in the left adrenal gland, with a maximum standardized uptake value of 70.1 (FIGURE 2).

FIGURE 1
Computed tomography revealed a mass in the left adrenal gland



The mass (arrow) measured 8.6 cm and was complex, hemorrhagic, and necrotic with attenuation of 33.1 Hounsfield units.

IMAGE COURTESY OF WALTER REED NATIONAL MILITARY MEDICAL CENTER, BETHESDA, MD

THE DIAGNOSIS

After appropriate preparation with alpha blockade (phenoxybenzamine 20 mg twice daily for 7 days) and fluid resuscitation (normal saline run over 12 hours preoperatively), the patient underwent successful open surgical resection of the adrenal mass, during which her blood pressure was controlled with a nitroprusside infusion and boluses of esmolol and labetalol. Pathology results showed cells in a nested pattern with round to oval nuclei

FIGURE 2

Another view of the adrenal mass



IMAGE COURTESY OF WALTER REED NATIONAL MILITARY MEDICAL CENTER, BETHESDA, MD

Intense radiotracer uptake (arrow) was present on positron emission tomography/computed tomography with contrast.

in a vascular background. There was no necrosis, increased mitotic figures, capsular invasion, or increased cellularity. Chromogranin immunohistochemical staining was positive. Given her resistant hypertension, clinical symptoms, and pathology results, the patient was given a diagnosis of pheochromocytoma.

DISCUSSION

Resistant hypertension is defined as blood pressure that is elevated above goal despite the use of 3 maximally titrated antihypertensive agents from different classes or that is well controlled with at least 4 antihypertensive medications.¹ The prevalence of resistant hypertension is 12% to 18% in adults being treated for hypertension.¹ Patients with resis-

tant hypertension have a higher risk for cardiovascular events and death, are more likely to have a secondary cause of hypertension, and may benefit from special diagnostic testing or treatment approaches to control their blood pressure.¹

There are many causes of resistant hypertension; primary aldosteronism is the most common cause (prevalence as high as 20%).² Given the increased risk for cardiovascular/cerebrovascular disease, all patients with resistant hypertension should be screened for this condition.² Other causes of resistant hypertension include renal parenchymal disease, renal artery stenosis, coarctation of the aorta, thyroid dysfunction, Cushing syndrome, paraganglioma, and as seen in our case, pheochromocytoma. Although pheochromocytoma is a rare cause of resistant hypertension (0.01%-4%),¹ it is associated with high rates of morbidity and mortality if left untreated and may be inherited, making it an essential diagnosis to consider in all patients with resistant hypertension.^{1,3}

■ **Common symptoms of pheochromocytoma** are hypertension (paroxysmal or sustained), headaches, palpitations, pallor, and piloerection (or cold sweats).¹ Patients with pheochromocytoma typically exhibit metanephrine levels that are more than 4 times the upper limit of normal.⁴ Therefore, measurement of plasma free metanephrines or urinary fractionated metanephrines is recommended.⁵ Elevated metanephrine levels also are caused by obesity, obstructive sleep apnea, and certain medications and should be ruled out.⁵

■ **All pheochromocytomas are potentially malignant.** Despite the existence of pathologic scoring systems^{6,7} and radiographic features that suggest malignancy,^{8,9} no single risk-stratification tool is recommended in the current literature.¹⁰ Ultimately, the only way to confirm malignancy is to see metastases where chromaffin tissue is not normally found on imaging.¹⁰

Pathologic features to look for include capsular/periadrenal adipose invasion, increased cellularity, necrosis, tumor cell spindling, increased/atypical mitotic figures, and nuclear pleomorphism. Radiographic features include larger size (≥ 4 -6 cm),¹¹ an ir-

➤ **Metastatic lesions can occur decades after resection, making long-term follow-up critical.**

regular shape, necrosis, calcifications, attenuation of 10 HU or higher on noncontrast CT, absolute washout of 60% or lower, and relative washout of 40% or lower.^{8,12} On MRI, malignant lesions appear hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging.⁹ Fluorodeoxyglucose avidity on PET scan also is indicative of malignancy.^{8,9}

■ **Treatment for pheochromocytoma** is surgical resection. An experienced surgical team and proper preoperative preparation are necessary because the induction of anesthesia, endotracheal intubation, and tumor manipulation can lead to a release of catecholamines, potentially resulting in an intraoperative hypertensive crisis, cardiac arrhythmias, and multiorgan failure.

Proper preoperative preparation includes taking an alpha-adrenergic blocker, such as phenoxybenzamine, prazosin, terazosin, or doxazosin, for at least 7 days to normalize the patient's blood pressure. Patients should be counseled that they may experience nasal congestion, orthostasis, and fatigue while taking these medications. Volume expansion with intravenous fluids also should be performed and a high-salt diet considered. Beta-adrenergic blockade can be initiated once appropriate alpha-adrenergic blockade is achieved to control the patient's heart rate; beta-blockers should never be started first because of the risk for severe hypertension. Careful hemodynamic monitoring is vital intraoperatively and postoperatively.^{5,13} Because metastatic lesions can occur decades after resection, long-term follow-up is critical.^{5,10}

■ **Following tumor resection**, our patient's blood pressure was supported with intravenous fluids and phenylephrine. She was able to discontinue all her antihypertensive medications postoperatively, and her plasma free and urinary fractionated metanephrine levels returned to within normal limits 8 weeks after surgery. Five years after surgery, she continues to have no signs of recurrence, as evidenced by annual negative plasma free metanephrines testing and abdominal/pelvic CT.

THE TAKEAWAY

This case highlights the importance of recognizing resistant hypertension and a potential secondary cause of this disease—pheochromocytoma. Although rare, pheochromocytomas confer increased risk for cardiovascular disease and death. Thus, swift recognition and proper preparation for surgical resection are necessary. Malignant lesions can be diagnosed only upon discovery of metastatic disease and can recur for decades after surgical resection, making diligent long-term follow-up imperative.

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