

## CLINICAL VIGNETTE

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# Is it a Pheochromocytoma? - Secondary Hypertension from Concurrent Adrenal Ganglioneuroma and Renal Artery Stenosis

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Dianne S. Cheung, M.D., MPH, and Terence Hammer, M.D.

### Case Presentation

A 71-year-old Caucasian female presented to establish primary care. Review of her general medical health revealed 80 pack per year smoking history and mild hypertension, controlled with losartan. EKG showed minor non-specific ST and T wave changes but no history of palpitations or chest pain. Labs including CBC, CMP, TSH, and urinalysis were all within normal limits. She had stopped smoking in 1973. Due to her extensive past smoking history, she underwent low-dose CT scanning to screen for lung cancer. CT showed no chest pathology but revealed an incidental 4.6x4.1x4.5 cm round left adrenal gland mass. She was referred to endocrine for further evaluation with concern for possible functioning adrenal adenoma.

Though she was diagnosed with hypertension more than 20 years ago, her blood pressure had progressively worsened over the last year. On physical exam, she was a well-developed, well-nourished female with BMI of 27 with unremarkable cardiac and pulmonary exams and no lower extremity edema. She was on losartan 100 mg daily and hydrochlorothiazide 25 mg daily was added. Despite two drug therapies, her systolic blood pressure ranged in the 160-190s mmHg, and her heart rate was in the 70-80s bpm range. However, she was asymptomatic and denied chest pain or shortness of breath.

Patient underwent biochemical testing to rule out hyperaldosteronism, pheochromocytoma, and adrenal Cushing's disease. Her aldosterone and renin came back normal, and her cortisol and ACTH levels were normal. However, her plasma free metanephrines were elevated at 1.9 with normal reference level <0.5 nmol/L. She underwent 24-hour urine testing with fractionated metanephrines and catecholamines at upper end of normal with repeat showing elevation less than 1.5 times the upper end of normal. A CT scan of the adrenal was done with adrenal protocol to measure Hounsfield units and time to wash out of contrast. Results of CT revealed a 5 cm solid mass in the left adrenal gland which, by enhancement and washout criteria and after contrast administration, was not typical for an adrenal adenoma. This CT scan was also followed by an MRI of the adrenal glands, which also showed a 4.6 cm left mass without significant drop out of phase image, making it atypical. The radiologist read the MRI for concern of possible metastasis versus adrenal

cortiocarcinoma rather than benign adenoma or pheochromocytoma.

Patient was referred to Endocrine Surgery, and given the high blood pressures and high plasma metanephrines, there was a high suspicion for pheochromocytoma despite non-convincing urine testing. The recommendation was for adrenalectomy after alpha blockade was achieved. The losartan and hydrochlorothiazide were discontinued, and phenoxybenzamine was started at 10 mg twice daily and titrated over several weeks to 40 mg twice daily. She did complain of lightheadedness; however, she was not orthostatic and tolerated alpha-blockade well. Patient reached the target blood pressure of <115/80 as recommended by Endocrine Surgery with heart rate of 61-80 bpm.

After 6 weeks of phenoxybenzamine alpha blockade, she underwent left adrenalectomy. Her surgery went well, and she had no post-operative complications. Her post-operative cortisol levels were normal; she did not have any complications with adrenal insufficiency. The final pathology was left 4 cm ganglioneuroma. At discharge from surgery, she was discontinued off of phenoxybenzamine and restarted on losartan 100 mg daily and hydrochlorothiazide 25 mg daily since her blood pressure did not immediately normalize post-surgery. However at home, patient regularly checked her blood pressures and noted decreasing postoperative blood pressures. She self-discontinued her hydrochlorothiazide and decreased her losartan to 50 mg daily. Over the course of 6-months post-surgery, her blood pressures remained stable with occasional spikes of her SBP, though usual range was 100-130/50-60. She required only single drug therapy for nearly a year with losartan only.

Approximately 1-year post adrenalectomy, she re-presented again to Endocrine with poorly controlled blood pressure. SBPs again were up to 160-190s, and DBP were in the 70-80s mmHg range. Her losartan 50 mg daily was increased to 100 mg daily, but after a few weeks, her blood pressure remained >150/90 and required addition of HCTZ 25 mg daily. With losartan-HCTZ 100-25mg daily, blood pressure remained in the 150-160/70-80 range and addition of amlodipine 5mg at bedtime was added to achieve blood pressures averaging

140/90. Again, there was a concern of recurrence of the ganglioneuroma or development of pheochromocytoma. However this time, urine biochemical testing for urine catecholamines, metanephrines, and plasma-free metanephrines were not elevated. A repeat CT scan showed evidence of left adrenalectomy and no mass in the right adrenal gland.

Secondary causes of hypertension were also considered, including renal artery stenosis. Doppler ultrasound showed slightly high velocities suggesting renal artery stenosis. MRA showed mild to moderate left renal artery stenosis. Patient wanted to avoid surgery, including stent placement in the renal artery, and wanted to continue with medical management to manage her blood pressure. She has since done well after limiting salt intake in her diet and increasing exercise. She is again off amlodipine and taking losartan HCTZ 100-12.5 mg daily.

## **Discussion**

### Is it a Pheochromocytoma?

Upon finding an adrenal adenoma and identifying hypersecretion of catecholamines in a patient with difficult to control blood pressure, the natural conclusion is to presume the patient has a pheochromocytoma and continue with the work-up. Classic triad for pheochromocytoma consists of episodic headache, sweating, and tachycardia. The blood pressure elevation can be paroxysmal or appear to be primary hypertension or essential hypertension that we typically encounter, thus making it difficult to tell if the patient may have pheochromocytoma based on blood pressure lability alone. Work-up for pheochromocytoma includes 24-hour urine collection for catecholamines and metanephrines, and the plasma-free metanephrine testing after which imaging is ordered. For the 24-hour urine testing, the general rule is for the urine catecholamines to exceed two-fold elevations above the upper limit of normal for the lab's reference range or elevated urine metanephrines (normetanephrines >900mcg/24 hr or metanephrines >400mcg/24 hr).<sup>1,2</sup> Plasma fractionated metanephrines, though easy to draw in the clinic, have high false positives (high sensitivity but low specificity), as patients with essential hypertension often have positive plasma fractionated metanephrine measures. The Mayo Clinic recommends further testing with imaging in the diagnosis algorithm if there is significant increase in plasma metanephrines (though how high has not been proposed) or when the degree of suspicion is high for pheochromocytoma such as in our patient with an adrenal mass and difficult to control blood pressure.<sup>2</sup> However in the outpatient setting, most patients present with just hypertension with low suspicion for pheochromocytoma and the recommendation is to start with the 24-hour urine collection, which has a high specificity and acceptable sensitivity<sup>1</sup> to avoid an excessive rate of false positives.

Localization follows with either abdominal MRI or CT scan of the adrenal glands. Both CT scan and MRI have high sensitivity (98-100 percent) but are only 70 percent specific due to high numbers of incidental benign adrenal lesions. CT scan with and without contrast with adrenal protocol measures

attenuation and time to washout IV iodine contrast. In a pheochromocytoma, there is increased attenuation on nonenhanced CT (>20 HU) and delay in contrast medium washout (10 minutes after administration of contrast, an absolute contrast medium washout of less than 50 percent). On MRI, there is high signal intensity on T2 weighted MRI. In our patient, the CT and MRI characteristics of the adrenal mass did not correspond to the CT or MRI guidelines. Since localization identified a mass in the left adrenal on both CT and MRI, more imaging was not done. However, if adrenal CT or MRI is negative in the presence of clinical and biochemical evidence of pheochromocytoma, then 123-I-metaiodobenzylguanidine (MIBG) scintigraphy may be performed. MIBG resembles norepinephrine, thus can be taken up by adrenergic tissue seen in pheochromocytoma. A MIBG scan can detect tumors not detected by CT or MRI or multiple tumors when CT or MRI is positive.<sup>2</sup>

The expectation prior to surgery was that this patient did indeed have a pheochromocytoma based on her symptoms, the elevations of her plasma metanephrines, and slight elevations of her urine metanephrines and catecholamines. However, her final surgical pathology of ganglioneuroma was unexpected.

### Ganglioneuroma what is that?

Presentation of adrenal ganglioneuromas can be very similar to pheochromocytoma as these lesions are quite large and can be found anywhere in the body since they are peripheral nerve tumors. Ganglioneuroma tumors originate from neural crest cells in the sympathetic ganglia or the adrenal medulla, but only 20% of ganglioneuromas occur in the adrenal adenoma.<sup>3</sup> Histologically benign, ganglioneuromas may evolve from differentiating neuroblastomas or may just be a primary tumor; however, ganglioneuromas are diagnosed generally at an older age than neuroblastomas.<sup>4</sup> However, 60% of ganglioneuromas occur in females before the age of 20 years. They are slow growing, and most patients are asymptomatic unless compression occurs to local structures in the abdomen or pelvis causing pain or constipation. On imaging, these tumors have homogenous borders that do not invade adjacent structures and contain calcium in 40-60% of cases.<sup>4</sup> In general, the tumors are non-secreting; however, there are some tumors that secrete catecholamines, and MIBG uptake may occur. In a study of 49 patients with primary ganglioneuroma in Germany, 57% of tumors accumulated 123I-MIBG.<sup>4</sup> Thus, it may be difficult to differentiate between a ganglioneuroma or a pheochromocytoma if the ganglioneuroma is secreting catecholamines as is the case in our patient.

### Renal artery stenosis

Interestingly, our patient also had renal artery stenosis, which likely caused her blood pressure to remain elevated post-adrenalectomy. In considering secondary causes of hypertension, renal artery stenosis should not be overlooked as it is far more common than pheochromocytomas or ganglioneuromas. Approximately 2-5% of Americans with hypertension suffer from renal artery stenosis (RAS), 90% due to atherosclerosis and 10% from fibromuscular hyperplasia (FMH).<sup>5</sup>

It occurs most commonly in patients over 45 with known atherosclerosis, but is also seen in women under 40 (FMH). The diagnosis is suggested by a rise in creatinine after starting an ACE inhibitor, presence of abdominal or renal bruits, and with elevated BUN/Creatinine. Confirmatory tests include renal US, CT angiography, MRA, or renal arteriography, which is the gold standard of diagnosis.

Treatment can include careful medical management, angiography with stenting, or surgical bypass. Medical and surgical treatments appear equally effective. Medical management includes treatment to control blood pressure and slowing the progression of kidney disease with the ACE inhibitors or angiotensin receptor blockers (ARBs).

In conclusion, our patient showed signs and symptoms of possible pheochromocytoma and was found to have a rare ganglioneuroma that even more rarely can behave like a pheochromocytoma by secreting small amounts of catecholamines and metanephrines. Thinking about other causes of hypertension was key since her “recurrence” of hypertension turned out to be concurrent renal artery stenosis rather than recurrent ganglioneuroma or pheochromocytoma. A remaining question was whether the presence of a ganglioneuroma on the left adrenal gland somehow caused the renal artery stenosis on the left renal artery, or was it just an unfortunate coincidence? An initial PubMed literature search did not yield adult cases with both ganglioneuroma and renal artery stenosis. However, there are reports of renal artery stenosis in patients with neurofibromatosis and hypertension suggesting the two secondary causes of hypertension can co-exist.<sup>6,7</sup>

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