**CLINICAL VIGNETTE**

# Pheochromocytoma in an Asymptomatic Patient

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***Case Presentation***

A 72-year-old male was initially seen by endocrinology for hypercalcemia. Evaluation revealed that patient had primary hyperparathyroidism and met criteria for surgical intervention. Pre-operative bedside thyroid ultrasound noted a hypoechoic mass in the left para-esophageal groove which was consistent with the findings of left thyroid lobe activity on parathyroid sestamibi scanning. Of note, no thyroid nodules were visualized. Parathyroidectomy showed the patient had hyperplasia of all four parathyroid glands with one of the glands being located within the thymus. A small portion of one of the parathyroid glands was reimplanted into the sternocleidomastoid muscle and a thymectomy was performed. Final pathology showed an involuted thymus. Subsequent parathyroid hormone (PTH) and calcium levels normalized after surgery and remained normal on follow up visits.

Eight years after surgery, the patient was found with microscopic hematuria on a routine physical. Computed tomography (CT) urogram showed a nonobstructive punctate stone in the right kidney as well as two left adrenal masses measuring 5.1 centimeters (cm) and 1.7 cm. Both masses were characterized as indeterminate. Abdominal magnetic resonance imaging (MRI) revealed two abutting enhancing T2 hyperintense left adrenal masses without macroscopic or microscopic fat measuring 4.7 and 1.9 cm. Radiology felt the masses were indeterminate, not classic for adenomas.

The patient was again evaluated by endocrinology and additional testing initiated for his incidental adrenal masses. Full endocrine review of systems was negative for any concerning symptoms. He specifically denied any sweats, headaches, palpitations, feelings of 'raciness' or 'jitters', weakness, weight loss or weight gain, or easy bruising. A review of his chart showed no history of hypertension or abnormal labs since his parathyroid surgery. The parathyroid surgery operative note reported that the surgery was uneventful with no reactions to anesthesia.

On exam, he appeared healthy with normal blood pressure and heart rate and his BMI of 22.8 $kg/m^2$. No facial fullness or dorsal adiposity was noted and there was no evidence of acanthosis nigricans. His thyroid exam was normal size without masses. His heart rate was normal with no murmur. Muscle strength and tone was normal. Laboratory analysis showed normal sodium, potassium, and calcium levels. Late night salivary cortisol levels, collected on three separate nights, were as follows: 0.058 µg/dL, 0.068 µg/dL, 0.079 µg/dL (upper limits of normal is 0.112 µg/dL). Upright aldosterone was 16 ng/dL (ref range 4 – 31 ng/dL) and renin was 2.1 ng/mL/hr (ref range 0.5 – 4.0 ng/mL/hr) with an aldosterone to renin ratio of 7.6. DHEA-S and 17-alpha-hydroxyprogesterone levels were also within normal range.

Plasma fractionated catecholamines were as follows:
Epinephrine 100 pg/mL (ref range 10-200 pg/mL)
Norepinephrine 6414 pg/mL (ref range 80-520 pg/mL)
Dopamine < 20 pg/mL (ref range 0-20 pg/mL)

Plasma fractioned metanephrines were as follows:
Free metanephrine 0.28 nmol/L (ref range 0-0.49 nmol/L)
Free normetanephrine 10.05 nmol/L (ref range 0-0.89 nmol/L)

In response to these labs, 24-hour urine catecholamines and metanephrines were collected with the following results:
Total urine volume 2394 mL
Creatinine 1293 mg (ref range 800-2100 mg/day)
Epinephrine undetected (ref range 1-14 µg/day)
Norepinephrine 1305 µg (ref range 14-120 µg/day)
Dopamine 225 µg (ref range 71-485 µg/day)
Metanephrine 196 µg (ref range 55-320 µg/day)
Normetanephrine 6258 µg (ref range 114-865 µg/day)

Although notorious for being difficult to interpret in the setting of neuroendocrine tumors, a chromogranin-A level was drawn and was 2088 ng/mL (ref range 0-103 ng/mL). Given these findings, a tentative diagnosis of pheochromocytoma was given.

With his history of hyperparathyroidism, there was a concern for possible multiple endocrine neoplasia type 2A. Despite a normal thyroid exam and prior normal thyroid ultrasound (eight years prior), another thyroid ultrasound was scheduled. It revealed two right sided thyroid nodules, 0.6 cm and 0.8 cm. The larger nodule was interpreted as "moderately suspicious". Concern for possible medullary thyroid cancer prompted a serum calcitonin level and fine needle aspiration (FNA). Calcitonin levels were normal and FNA of the 0.8 cm nodule yielded a Bethesda category II benign nodule.

Further imaging with PET-CT using DOTATATE revealed DOTATATE uptake within the region that correlated with the

known left adrenal masses as well as T8, L2, L4, and S1 vertebral bodies. At radiology's recommendation an MRI was performed to better evaluate the vertebral bodies. The imaging results were suggestive of neoplastic metastatic disease. The patient was sent for surgical consultation and adrenalectomy was recommended. He was started on phenoxybenzamine at 10mg twice a day for fourteen days prior to his surgery despite having no history of hypertension or symptoms suggestive of episodic hypertension. The patient tolerated surgery well without complications. Final pathology confirmed pheochromocytoma but was an encapsulated solitary mass measuring 6.4 cm rather than two separate smaller masses. Urine metanephrines were repeated two months after surgery and with the following results:

Total urine volume 1607 mL
Creatinine 1189 mg (ref range 800-2100 mg/day)
Metanephrine 122 µg (ref range 55-320 µg/day)
Normetanephrine 464 µg (ref range 114-865 µg/day)

Given the normalization of his urine normetanephrine and full recovery, surgery was deemed successful. The patient was diagnosed with malignant pheochromocytoma with suspected metastasis limited to his spine based on imaging and is currently being followed with serial imaging and labs. The patient consulted with a medical geneticist and was negative for mutations for SDHA/B/C/D. He continues to be asymptomatic, specifically denying any bone pain.

***Discussion***

Pheochromocytomas are catecholamine-secreting tumors that are derived from chromaffin cells within the adrenal medulla. Catecholamines consist of epinephrine, norepinephrine, and dopamine. The incidence is highest between age 40s and 50s but may arise at any age.[1] Over half of pheochromocytomas occur sporadically without a hereditary link and are usually unilateral. Those with familial pheochromocytomas, tend to have bilateral tumors. Sporadic pheochromocytomas are often found incidentally on imaging. The majority of familial disorders are associated with multiple endocrine neoplasia type 2 (MEN 2), where patients can develop the constellation of endocrinopathies of primary hyperparathyroidism, medullary thyroid cancer, and pheochromocytoma. A smaller percentage of familial pheochromocytoma can be associated with von Hippel-Lindau (VHL) disease.

The classic symptoms of pheochromocytoma are intermittent headaches, palpitations/tachycardia, and excessive sweating. This triad taught in medical training, but a review of case reports noted that only 24% of patients with pheochromocytoma had these symptoms.[2] Hypertension was found in about 60% of cases – keeping in mind that the incidence of pheochromocytoma is 0.2% in patients with high blood pressure.[3] Hypertension in the setting of pheochromocytoma tends to be episodic and is considered the most common symptom. About 15% of patients will have normal blood pressure. Normal blood pressure is more common in patients with pheochromocytoma found incidentally via imaging for other reasons, representing over half of newly diagnosed pheochromocytoma cases.[2] For those with symptoms, headaches tends to be the common complaint in 90% of symptomatic cases, as well as episodic sweats in 70% of cases. Palpitations can occur in response to headaches or sweats, but may also be an isolated symptom.[4] Patients with familial pheochromocytoma, as part of MEN 2, have the triad of symptoms in about 50% of the time with about 30% having hypertension.

About 60% of pheochromocytomas are discovered as an incidental finding on imaging.[5] It is important to detect this disease early because of the high morbidity and mortality associated with catecholamine hypersecretion. Detecting hereditary cases early can also help diagnose affected family members.

The diagnosis of pheochromocytoma must be made biochemically. It is defined as the hyperproduction of catecholamines, two of which, in turn are metabolized within the tumor to metanephrines: metanephrine (derived from epinephrine) and normetanephrine (derived from norepinephrine). It is possible to produce excessive catecholamines while only hyper secreting the metabolite metanephrines. Because of this, measuring fractionated metanephrines is the preferred screening test for suspected pheochromocytoma over fractionated plasma catecholamines. The negative predictive value of plasma fractionated metanephrines is high with normal levels able to rule out pheochromocytoma in most patients.[4] A database review showed that plasma fractionated metanephrines have a high sensitivity (95-100%) but have a low specificity (85%).[6] The same study reported 97% of patients with high blood pressure who had elevated plasma fractionated metanephrines did not have pheochromocytoma. When measuring plasma fractionated metanephrines, it is recommended that the patient remain supine for 30 minutes before sampling as seated samples can result in up to a 3-fold increase in false-positives.[3]

If plasma fractionated metanephrines are elevated or are normal, with persistent high suspicion for pheochromocytoma, 24-hour urine fractionated catecholamine and metanephrines should be assessed next. High-performance liquid chromatography (HPLC) or tandem mass spectroscopy (MS/MS) are the preferred laboratory methods to measure urine metanephrines. As most modern laboratories use either one of these methods, it is usually not necessary to specify these methods exactly. It is important to also measure 24-hour urine creatinine to ensure adequate urine collection. Urine fractionated catecholamines and metanephrines have an estimated 98% sensitivity and 98% specificity in making the diagnosis of pheochromocytoma.[4] Although urine fractionated metanephrines have the highest yield in assessing for pheochromocytomas, it also recommended to measure urine fractionated catecholamines to detect the rare tumors that selectively hyper-secrete dopamine.

When assessing for pheochromocytoma, it is important to ensure patients are not taking medications that could falsely elevate catecholamines or metanephrines. Although not an

exhaustive list, the following are common medications or substances to consider:

- Alcohol
- Amphetamines
- Buspirone
- Levodopa
- Phentermine
- Reserpine
- Tricyclic antidepressants

Once pheochromocytoma is confirmed biochemically, in patients not previously identified via incidental radiological findings, imaging studies should be pursued next. Although the majority of pheochromocytomas are found within the adrenal gland, 15% of tumors can be extra-adrenal. Of these, 75-85% are located infra-diaphragmatic in the para-aortic region, up to 10% in bladder or thorax, and rarely in the skull base or pelvis.[7] As such, CT or MRI of the chest, abdomen, and pelvis is recommended. Both CT and MRI have up to 100% sensitivity and 70% specificity.[4] The lower specificity is due to the incidence of adrenal incidentalomas. CT imaging has the advantage over MRI in distinguishing between two closely spaced objects as separate entities. However, MRI does not expose patients to radiation and can discern pheochromocytomas from other adrenal masses using T-2 weighted images. It is up to the clinician to determine which of the two imaging modalities is appropriate.

If CT or MRI fails to detect any masses and the suspicion for pheochromocytoma remains high or the imaging is suggestive of metastatic disease, total body nuclear imaging studies should be considered. Gallium-68 (Ga-68) DOTATATE positron emission tomography (PET) is the preferred modality. DOTATATE binds to the overexpressed somatostatin receptors on neuroendocrine tumor cells, allowing these tumors to be visualized with PET imaging. Taking advantage of the hypermetabolic nature of cancer as compared to normal cells, fludeoxyglucose (FDG), a radioactive glucose molecule, is another option for PET scans when assessing for metastatic disease. One more PET modality uses flourodopa (FDOPA), a dopamine analogue, as a marker to detect neuroendocrine tumors. Of the three PET options, DOTATATE has the high sensitivity for pheochromocytoma although, as with most diagnostic imaging, each has its own advantages.[4] If PET imaging is not helpful, scintigraphy with $^{123}$I-metaiodobenzylguanidine (MIBG), a norepinephrine analogue, may be used to find otherwise undetected tumors. Although MIBG has a specificity for pheochromocytoma of 70-100%, its sensitivity of 85-88% along with a lower spatial resolution makes it less preferable to PET modalities following negative CT or MRI studies.[3]

With the diagnosis of pheochromocytoma confirmed, surgical removal of the tumor is recommended. It is imperative to control hypertension perioperatively to prevent cardiovascular complications, such as hypertensive crisis, during surgery. The suggested method is to use α-adrenergic receptor blockers for 7-14 days leading up to surgery.[4] The preferred drug is phenoxybenzamine, a nonspecific α-adrenergic receptor blocking agent. Due to lower costs and better tolerability, some centers use selective α-1-adrenergic blockers such as terazosin or doxazosin. Because high levels of catecholamines can induce volume contraction and α-adrenergic blockade can lead to orthostatic hypotension, patients also advised to initiate a high sodium diet (5000mg daily). If present, tachycardia can be managed with β-adrenergic receptor blockers but only after the patient has had substantial exposure to α-adrenergic blockers. Is it imperative never to start β-adrenergic blockers before initiating α-adrenergic blockers as unopposed stimulation of α-adrenergic receptors can result in paradoxical hypertension with the potential for hypertensive crisis. If blood pressure remains uncontrolled, calcium channel blockers may be added.

For sporadic pheochromocytoma which tend to be unilateral and intra-adrenal, minimally invasive adrenalectomy is the preferred surgical approach. Patients with familial pheochromocytoma, such as MEN2 or VHL, are more at risk for bilateral adrenal involvement. Hence, bilateral adrenalectomy may be indicated with subsequent life-long glucocorticoid therapy. In this scenario, adrenal-cortex sparing surgery may be attempted but often yields disappointing results.

Genetic testing is recommended in all patients with pheochromocytoma and is usually reserved until after the diagnosis has been confirmed on pathology. Although most cases are sporadic, about 40% of pheochromocytoma tumors are associated with a familial disorder – such as MEN2, VHL, or neurofibromatosis type 1 (NF1). As such, patients should be referred to a clinical geneticist.

Recurrence of pheochromocytoma has been estimated to be between 3% and 16%.[3] Familial pheochromocytoma predisposes to higher risk of recurrence as dose having extra-adrenal tumors. Long-term surveillance for all patients is advised with intermittent biochemical testing.

About 10% of pheochromocytomas are malignant.[8] The distinction between benign and malignant pheochromocytoma cannot be made biochemically or histologically. The only defining criteria is the presence of metastasis in malignant disease. Bones are the most common sites for metastasis and rarely spread to lungs, liver, or lymph nodes.[9] Risk for malignancy increases with familial pheochromocytoma, presence of SHDB gene mutation, and larger tumors. In one report, 70% of patients with metastatic pheochromocytoma had indolent disease.[10] The prognosis of malignant pheochromocytoma varies considerably. Most five-year survival rates vary from 60-85% with a few studies reporting 35%.[11] Surgical resection of the primary tumor and subsequent biochemical normalization are associated with improved outcomes as well as normalization of blood pressure and lack of metastasis to large organs.[8]

Our patient's presentation reaffirms that most pheochromocytomas are found incidentally while his lack of symptoms and

physical findings highlights the difficulties with diagnosing this condition. And although he has evidence of bone metastasis, which tends to carry a poorer prognosis, his outcome is considered favorable given his disease is sporadic, his metanephrines normalized postoperatively, and he continues to feel well.

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