Pheochromocytoma Diagnosis After an Abnormal Stress Test: Case Report and Review of the Literature

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Pheochromocytoma is a rare adrenal gland tumor that is often difficult for physicians to diagnose because of its general, nonspecific complaints. Diagnosis is particularly difficult in patients with neurofibromatosis 1, because pheochromocytoma in these patients will mimic other cardiovascular abnormalities. The authors report the case of a 60-year-old woman with an extensive history of hyperlipidemia, malignant hypertension, coronary artery disease, and neurofibromatosis 1 who was referred for an elective cardiac catheterization as a result of an abnormal stress test. The patient returned to the hospital 3 days after the procedure complaining of increased angina and palpitations. While hospitalized, she developed severe episodic hypertension. A computed tomographic scan revealed bilateral adrenal masses. Findings of biochemical and imaging evaluation confirmed the diagnosis of bilateral pheochromocytoma. Early screening of pheochromocytomas in high-risk populations is essential for prompt diagnosis and successful management.

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Pheochromocytoma is a rare adrenal gland tumor with an estimated incidence of 1 to 2 per 100,000 persons.[1] Many high-risk patients with pheochromocytoma will initially present to their primary care physician with general, nonspecific complaints that may not lead physicians to consider pheochromocytoma in their initial differential diagnosis. Diagnosis is particularly difficult in patients with neurofibromatosis 1 (NF1), an autosomal dominant genetic disorder that affects nearly 1 in 3500 persons,[2] because pheochromocytoma in these patients will mimic other cardiovascular abnormalities. Early identification and surgical removal of pheochromocytoma in patients with NF1 is essential for preventing unnecessary and sometimes fatal hemodynamic complications during future unrelated surgeries.

We report the case of a 60-year-old woman who was found to have pheochromocytomas after presenting with chest palpitations. This case highlights the importance of diagnosing pheochromocytomas early, because although it is rare, it can be life threatening if left undiagnosed.

Report of Case

A 60-year-old woman presented to the emergency department with chest palpitations that had worsened over the course of the previous 6 months. Cardiac evaluation revealed abnormal stress test findings, leading to the diagnoses of unstable angina, coronary artery

disease, hypertension, and hyperlipidemia. Cardiac catheterization with angioplasty was performed, and a left anterior descending stent was placed 4 days later. The patient returned to the emergency department 4 days after stent placement describing increasing palpitations accompanied by heaviness in her chest, which lasted from 2 to 20 minutes. She was admitted to the hospital.

Before her initial visit to the emergency department, the patient had severe episodic hypertension accompanied by heaviness in her chest, palpations, sweating, flushing, shortness of breath, and tinnitus. The patient had a medical history of neurofibromatosis that was diagnosed early in her life, hyperlipidemia, uncontrolled hypertension, coronary artery disease, and acute myocardial infarction in 2010 (3 years before current hospital admission). Her medications before admission were as follows: aspirin (81 mg), ranolazine (500 mg), simvastatin (20 mg), prasugrel (10 mg), carvedilol (25 mg), omeprazole (20 mg), vitamin B_{12} (500 µg), and nitroglycerin (0.4 mg). The patient had a surgical history of hysterectomy, cholecystectomy, and tubal ligation. In addition, a second cardiac catheterization was performed the day of hospital admission to assess the patency of the newly placed stent. On admission, her vital signs were as follows: heart rate, 84/min; blood pressure, 128/82 mm Hg; respirations, 16/min; and oxygen saturation, 97% while breathing room air.

Initial laboratory test results revealed an elevated white blood cell count of 12,000/µL (reference range, 4500-11,000/µL), an elevated serum chloride level of 112 mmol/L (reference range, 96-106 mmol/L), an elevated glucose level of 132 mg/dL (reference range, 70-110 mg/dL), and troponin levels within reference range. The patient's lactate level was also elevated at 2.6 mmol/L (reference range, 0.6-1.7 mmol/L). Previous research[3] has shown that high lactate levels in patients who present with symptoms similar to our patient may be associated with underlying pheochromocytomas. All other laboratory values were within reference range. An electrocardiogram showed nonspecific anterolateral ST-T changes. Findings on myocardial perfusion imaging with regadenoson showed perfusion defects in the anterior and lateral walls, and subsequent cardiac catheterization revealed patency of the recently placed stent and no new lesions.

Three days after admission, the patient was transferred to the critical care unit because of severe hypertension associated with chest pain, palpitations, sweating, flushing, shortness of breath, and tinnitus. Vital signs at the time of critical care unit admission were as follows: heart rate, 108/min; blood pressure, 224/150 mm Hg; respirations, 20/min; oxygen saturation, 98% while breathing room air; and temperature, 97.5°F. During the hospital stay, the patient continued aspirin, ranolazine, omeprazole, prasugrel, and carvedilol therapy; other medications were clonidine (0.1 mg), hydralazine (50 mg), atorvastatin (40 mg), lisinopril (20 mg), ondansetron (4 mg), and hydrocodone bitartrate/acetaminophen (5/162.5 mg). Sodium nitroprusside treatment was also initiated, and clonidine was discontinued when she was admitted to the critical care unit for monitoring due to her hypertensive urgency. A workup to rule out pheochromocytoma was started. Results of a serum-free metanephrine and plasma catecholamine panel showed an elevated level of substantial increase in normetanephrine, plasma free at 6.0 nmol/L (reference, <0.9 nmol/L) and metanephrine, plasma free at 5.8 nmol/L (reference, <0.50 nmol/L). Catecholamine panel findings showed an elevation in plasma dopamine at 93 pg/mL (reference range, 0-20 pg/mL), epinephrine at 1714 pg/mL (reference range, 10-200 pg/mL), and norepinephrine at 4035 pg/mL (reference range, 80-520 pg/mL). A 24-hour urine of vanillylmandelic acid was also elevated at 22.2 mg/24 h (reference range, 0.2-7.7 mg/24 h).

Abdominal computed tomography (CT) findings revealed bilateral adrenal masses (*Figure*). The

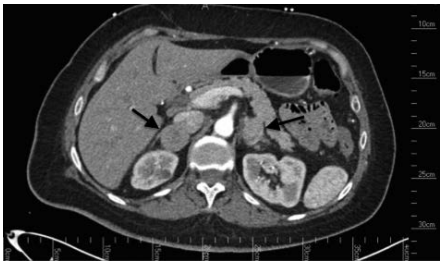

Figure.
Computed tomographic image of the abdomen identifying bilateral adrenal masses in a 60-year-old woman with severe episodic hypertension, palpations, sweating, flushing, shortness of breath, and tinnitus.

largest right adrenal mass measured 3.1 cm at its largest diameter and 54 Hounsfield units (HU) on a precontrast CT scan. After contrast administration, the lesion measured 70 HU, and after a 10-minute delay, the lesion measured 57 HU. The largest left adrenal mass measured 3.0 cm and 46 HU on a precontrast CT scan. Immediately after contrast administration, the mass measured 87 HU, and after a 10-minute delay, the mass measured 58 HU.

The presence of the bilateral adrenal masses and laboratory data indicating an elevation in catecholamines prompted an iodine 123 (^{123}I) metaiodobenzylguanidine (mIBG) study for localization of pheochromocytomas. The literature has reported the 22-hour mIBG scan to have a sensitivity of 1.00 and a specificity of 0.95, as well as a positive predictive value of 0.95 and a negative predictive value of 1.00.[4] Before the study, the patient was given a 0.15-mL oral solution of potassium iodine. Whole-body CT scans were obtained at 4 and 24 hours after the patient received the 4.8-mCi ^{123}I mIBG injection. The results showed focal abnormal radiotracer uptake in regions corresponding to the left and right adrenal glands, which in correlation with previous CT findings were consistent with the diagnosis of bilateral pheochromocytoma. The patient's blood pressure was optimized, and she underwent a successful bilateral adrenalectomy. She continues to follow up with her primary care physician and has yet to report any recurrent or new related symptoms.

Discussion

Pheochromocytoma typically manifests as a triad of symptoms: sweating, headache, and palpitations.[5] When patients present with this triad accompanied by persistent hypertension or fluctuating blood pressure, it is important to remember that pheochromocytoma, although rare, should be included in the physician's differential diagnosis list. However, the level of suspicion should be left to the physician's discretion, as the rarity of pheochromocytoma does not make it worthwhile to screen every patient who comes to the office with these symptoms.

Ueda et al[6] found that 0.1% of patients who are evaluated for chronic hypertension are found to have pheochromocytoma. However, research[7] has shown that because of the infrequency of screening for pheochromocytoma, previous incidence data may not be fully representative of the true occurrence of pheochromocytoma in patients with hypertension. Furthermore, a 2013 study[8] found that of 57 confirmed cases of pheochromocytoma, 40 (70%) were found during an imaging study not related to the diagnosis of pheochromocytoma or its related symptoms. Additionally, a 50-year review[9] of autopsy-proven pheochromocytoma cases revealed that 41 of 54 cases (76%) were diagnosed during postmortem examination after not being considered initially. The serendipitous discovery of pheochromocytoma is becoming more common because the use of cross-sectional imaging is becoming more regular.

Traditionally, pheochromocytomas have been said to follow the "rule of 10s": 10% of tumors are bilateral, 10% are extra-adrenal, 10% are familial, and 10% are malignant.[10] Advances in genetics and diagnostic testing have challenged this rule, however.[10] Prevalence of bilateral adrenal tumors is higher than 10% in some familial pheochromocytoma syndromes, and although previous literature has cited the genetic component of pheochromocytomas at roughly 10%, recent data suggest that as

many as 24% to 50% of confirmed pheochromocytomas may have a genetic component.[1,5,11]

In a review of current genetic familial syndromes associated with the development of pheochromocytoma, Adler et al[5] found that patients with an autosomal dominant familial history of von Hippel-Lindau disease, multiple endocrine neoplasia type 2, NF1, or hereditary paraganglioma syndrome have an increased risk of developing pheochromocytoma. Specifically, patients with NF1 have an autosomal dominant mutation of the tumor suppressor gene at chromosome 17q11.2.[12] This mutation occurs in 1 of 3500 people worldwide and has the highest new mutation rate among autosomal dominant disorders.[12] In patients with NF1, pheochromocytoma is known to occur at a rate of 0.1% to 5.7%.[12] This incidence increases to 20% to 50% in patients with diagnosed NF1 who also have hypertension.[12] These data are important for primary care physicians because although the mean age of patients receiving a pheochromocytoma diagnosis is 44 years in sporadic cases, the mean age of patients receiving a diagnosis is 25 years in cases with a genetic component (or suspected genetic component).[13]

The presence of NF1 makes the diagnosis of pheochromocytoma difficult because NF1-related vasculopathy and renal artery stenosis can lead to vessel changes that will in turn alter the control of blood pressure. Pheochromocytoma in a patient with NF1 will mimic other cardiovascular abnormalities, making diagnosis particularly difficult in patients with comorbid heart conditions.

Early and accurate diagnosis of pheochromocytoma is necessary for successful management and removal. An updated and more inclusive screening tool for pheochromocytoma is now available to physicians. In 2005, the first international pheochromocytoma symposium generated the following criteria for considering genetic testing: relevant family history; age younger than 35 years; and multifocal, extra-adrenal, or malignant disease.[14] Patients with NF1, especially those with hypertension, should be monitored more closely and receive annual plasma-free metanephrine screening. Although this guideline may be cost prohibitive in some situations, it should be adhered to with patients who have a confirmed history of genetic predisposition or suggestive symptoms. A proposed algorithm can be found in the ninth edition of *Greenspan's Basic and Clinical Endocrinology*.[15] Because familial pheochromocytoma generally presents at an earlier age than sporadic pheochromocytoma, general practitioners, family physicians, and other primary care physicians should consider the tumor in patients with a known history of 1 of the previously mentioned genetic disorders who also exhibit 1 or more of the signs and symptoms of pheochromocytoma.

Conclusion

As with the present case, many high-risk patients with pheochromocytoma will initially present with general, nonspecific complaints that may not lead physicians to consider pheochromocytoma on their initial differential diagnosis. Early diagnosis and treatment is imperative to circumvent life-threatening complications. Awareness of the connection between early age of presentation, genetic association, and the related cardiovascular signs and symptoms will allow primary care physicians to better detect, diagnose, and manage pheochromocytoma.

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