REVIEW ARTICLE

Pheochromocytoma

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Pheochromocytoma is a catecholamine secreted tumor, which is derived from chromaffin cells. These tumors are estimated to occur in 2-8 out of 1 million people per year. In this case, a 50-year-old Caucasian female presented to a primary care physician's office with a 10-year history of symptoms that were solely attributed to a diagnosis of atrial fibrillation and CREST syndrome. This case illustrates the importance of a thorough workup in patients with seemingly common recurrent medical complaints. Earlier investigation could have led to earlier treatment and resolution of the patient's symptoms. As family physicians, we are the front line when it comes to diagnosing and it is important to do our own investigation and not rely solely on the previous work of others.

BACKGROUND

Pheochromocytoma is a rare, catecholamine-secreting tumor that arises from the chromaffin cells of the adrenal medulla. If the tumor is found outside of the adrenal gland, it is called a paraganglioma and arises from the sympathetic ganglia. Fränkel first recognized the tumor in 1886 and Ludwig Pick later coined "pheochromocytoma" in 1912 from the Greek words phaios ("dusky"), chroma ("color"), and cytoma ("tumor"). These words describe the black-colored staining reaction caused by the oxidation of catcholamines when they are exposed to dichromate salts.[1,2]

Pheochromocytoma is normally a benign mass with an annual incidence of 2 to 8 cases per 1 million people. It occurs in equal frequency between men and women and in the fourth or fifth decade. A "rule of 10" has been described: 10% are extra-adrenal, 10% occur in children, 10% are multiple or bilateral, 10% recur after surgical removal, 10% are malignant, 10% are familial, and 10% of benign sporadic adrenal pheochromocytomas are found as adrenal incidentalomas.[2] However, new evidence suggests the percentage of familial pheochromocytoma to be higher. Those with familial pheochromocytoma generally present earlier in life and have some sort of germline mutation. There are four autosomal dominant genetic syndromes that are closely associated with pheochromocytoma: Multiple Endocrine Neoplasia Type 2A (MEN2A), Multiple Endocrine Neoplasia Type 2B (MEN2B), von Hippel-Lindau Disease (VHL), and Neurofibromatosis Type 1 (NF1).

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MEN2A or Sipple's syndrome occurs in about 1 in 35,000 people. All have medullary thyroid cancer (MTC), half have pheochromocytoma, 20% have primary hyperparathyroidism and about 5% have cutaneous lichen amyloidosis. MTC is typically diagnosed before the pheochromocytoma is present. The mutations responsible for MEN2A in the RET proto-oncogene.

MEN2B also has a mutation in the RET proto-oncogene except it is a missense mutation MEN2B patients also have similar characteristics to the MEN2A individuals: all have MTC and half have pheochromocytoma. But, MEN2B patients may also have mucocutaneous neuromas, skeletal deformities, joint laxity, myelinated corneal nerves, and Hirschsprung's disease (intestinal ganglioneuromas).[2] Interestingly, the MEN2 syndrome pheochromocytomas produce overall higher levels of catchecolamines and their metabolites due to PMNT overexpression and increased tyrosine hydroxylase activity. They also secrete primarily epinephrine and metanephrine when compared to the other syndromic pheochromocytomas.[2]

VHL patients can present with a wide spectrum of benign or malignant neoplasms. It occurs in 1 out of 35,000 people and is caused by a loss of function of the VHL tumor suppressor gene. Those with type 2C have the highest risk for developing pheochromocytoma. About 98% of those with VHL syndrome that develop pheochromocytoma have a missense mutation in the VHL gene and produce predominantly norepinephrine and normetanephrine due to PMNT underexpression.[2]

NF1 has various expression profiles and most commonly presents with café-au-lait spots, neurofibromas, axillary and inguinal freckling and Lisch nodules (iris hamartomas). Only 2% of those with NF1 develop pheochromocytomas, which are normally solitary and benign. Approximately 1 in 3,000 people develop NF1 and it is caused by a loss of function mutation in the NF1 tumor suppressor gene.

Genetic testing should be made available to those who are diagnosed with pheochromocytoma and the following genes should be ordered sequentially based on the presenting symptoms. Testing should also be made available to their family members as well as genetic counseling to understand the syndrome and the risks associated with it.[2]

CLINICAL PRESENTATION

Pheochromocytoma normally presents with hypertension and an episodic complaint of headaches, palpitations, and profuse sweating known as the "classic triad."[1] Hypertension is the most pertinent and serious symptom and can eventually lead to hypertensive crisis, which can result in heart failure, pulmonary edema, arrhythmias, intracranial hemorrhage and death. However, if the tumor is diagnosed early the patient can have a normal blood pressure and for this reason it is known as the "great masquerader."[1]

The episodes are attributed to the paroxysmal release of catecholamines, chronic volume depletion, impaired sympathetic reflexes and altered sympathetic vascular regulation.[2] Also causing the episodes are positional changes, surgery, exercise, pregnancy, urination, medications (metoclopramide, opiates, tricyclic antidepressants, B-andrenergic antagonists, anesthetic agents), anxiety, and maneuvers that increase intra-abdominal pressure (lifting, defecation, colonoscopy, endoscopy, trauma).[1,2] Furthermore, tumor manipulation and ingestion of food or beverages that contains tyramines can cause the episodes.[3] The episodes typically last 15-20 minutes however some people have shorter or longer durations but typically last less than an hour.[1,2] The frequency of spells varies per person: some have multiple episodes a day or monthly episodes.

During the episodes, patients can become anxious and pale, tachycardic, and have palpitations.[1,2] Other symptoms include a forceful heartbeat, facial pallor, cold hands and feet, and tremor, which are caused by the peripheral vasoconstriction. Some patients describe the episode as starting with a sudden "rush" in the chest, shortness of breath, followed by a forceful heartbeat and throbbing headache. At the end of the spell, the patient can experience the increased body heat and sweating.[2]

Other nonspecific signs of pheochromocytoma include hypertensive retinopathy, angina, nausea, constipation, hyperglycemia, diabetes mellitus, Raynaud's phenomenon, livedo reticularis, erythrocytosis, mass effects from tumor,[2] lassitude, heat intolerance, nervousness, fever, abdominal pain,[4] dyspnea, weight loss, visual disturbances, and mental problems.[3] These episodes can also lead to orthostasis especially in epinephrine and dopamine dominant pheochromocytomas.[2]

DIAGNOSIS

The diagnosis of pheochromocytoma is made first by biochemical evaluation and then by radiological imaging for tumor localization. Biochemical evaluation is based on the measurement of catecholamines, methylated metabolites, and metanephrines secreted in the urine or plasma. After the sample is collected, it is analyzed via high-performance liquid chromatography with electrochemical detection or tandem mass spectrometry.[2]

All sources agree that the plasma collection method is easier and more convenient for catecholamine and metanephrine detection but there are discrepancies about its sensitivity compared to the 24-hour urinary collection method.

Neuman[1] and Mittendorf[4] agree that the plasma test is superior and specifically, the plasma metanephrine test is the best test to use to confirm or exclude a diagnosis of pheochromocytoma. Pheochromocytomas metabolize catecholamines constantly and thus, the concentration of metanephrines should be consistently high whereas the measurement of catecholamines will have more of an episodic elevation. Therefore, the clinician would have to measure catecholamines when a patient is having an episode in order to get a valid collection creating quite a challenge since it is hard to predict an episode and harder to schedule for that.[4] Lenders[5] and colleagues concluded more diagnoses of pheochromocytoma were ruled out in patients by the plasma free metanephrines test compared to the urinary measurement when both have a high sensitivity. Therefore, they suggested the plasma free metanephrines should be used as the first choice test for all pheochromocytoma evaluations.[5] Further support from Neuman[1] states the plasma free metanephrines are less susceptible to false-positives like elevations from stress, which will normally cause high catecholamine and metanephrine levels. Studies at the National institutes of health (NIH) also confirm plasma free metanephrines as the superior test with a sensitivity of 98% and a specificity of 92%.[3] Sawka and colleagues recommend performing a 24-hour urinary total metanephrines and catecholamines for low-risk patient because it has less false-positives and will be efficient at excluding the diagnosis. For high-risk patients, they suggest measuring plasma metanephrines. Clinicians at MD Anderson also prefer the plasma metanephrine testing because it is easier for the patient and more sensitive.[3] Finally, others suggest using both if possible.[3]

To perform either the plasma or the urine collection measurements, patients must not be taking tricyclic antidepressants, levodopa, sympathomimetics, diuretics, alpha and beta blockers or on a diet (mainly tyramines) because these can all cause false-positives.[1] It is recommended

CASE REPORT

Presentation

A 50-year-old female presented as a new patient to her physician's office with a complaint of worsening palpitations over the last 6 months. The patient stated that the palpitations had become almost constant with uncontrollable sweating. She also noted intermittent episodes of headaches, all of which improved with over the counter medications. She denied any chest pain or shortness of breath.

History

Her palpitations first began 10 years prior and at that time she was diagnosed with atrial fibrillation. Over the past 10 years, the patient had multiple follow up appointments with her primary care physician as well as her cardiologists and mentioned to them that she felt the palpitations were increasing in frequency. She also noted on multiple occasions that she would find herself sweating, even in a cool temperature. The patient's past medical history was remarkable for hypertension, hyperlipidemia, and CREST syndrome. Upon physical exam, the patient was noted to be a fit-appearing female in no acute distress. Vital signs showed a blood pressure of 128/70 mmHg, heart rate of 74 beats per minute, and a respiratory rate of 12. Cardiac examination demonstrated an irregularly irregular heartbeat. Skin exam showed mild pallor to her fingertips. An electrocardiogram was performed in office, which displayed atrial fibrillation with a heart rate of 128 beats per minute. The patient was referred to cardiology with a plan for a possible electrophysiology study.

Laboratory/Imaging

Laboratory tests were also ordered for the patient as well as an echocardiogram and a chest x-ray. The chest x-ray showed no acute cardio-pulmonary disease, while the echocardiogram showed no evidence of heart failure. Initial laboratory results are seen in Table 1. 24-hour urine Vanilylmandelic acid showed 12.4 mg/24hr (normal is < or = 6.0 mg/24hr), which is twice the normal value. Urine Norepinephrine (NORE) showed a level of 538 mcg/24hr (normal: 15-100 mcg/24hr), urine Epinephrine (EPI) had a level of 50 mcg/24hr (normal: 2-24 mcg/24hr), while the urine total catecholamines (NORE + EPI) had a level of 588 mcg/24hr (normal: 26-121 mcg/24hr). Urine normetanephrines (NORM) showed a value of 2,225 mcg/24hr (normal: 52-310 mcg/24hr), urine Metanephrine (MET) showed a value of 564 mcg/24hr (normal: 19-140 mcg/24hr), and the urine total metanephrines (NORM + MET) value is 2,789 mcg/24hr (normal: 95-475 mcg/24hr). The Plasma free metanephrine (PMET) levels are 44 pg/ml (normal: < or = 57 pg/ml), plasma free normetanephrines (PNORM) is 607 pg/ml (normal: < or = 148 pg/ml), and the plasma free total metanephrines (PMET + PNORM) are 651 pg/ml (normal: < or = 651 pg/ml).

The chest x-ray revealed a nodular density in the apex of the left lung, for which a Computed Tomography (CT) Scan was ordered. The CT scan failed to locate any nodules or masses in the lung, however, an incidental finding of a 3 centimeter mass

Table 1: Laboratory Results

Test Name	Value	Reference Range
24 hour urine Vanillylmandelic acid	12.4mg/24hr	< or = 6.0mg/24hr
Urine Norepinephrine (NORE)	538mcg/24hr	15-100mcg/24hr
Urine Epinephrine (EPI)	50mcg/24hr	2-24mcg/24hr
Urine Total Catecholamines (NORE+EPI)	588mcg/24hr	26-121mcg/24hr
Urine Normetanephrimes (NORM)	2225mcg/24hr	52-310mcg/24hr
Urine Metanephrine (MET)	564mcg/24hr	19-140mcg/24hr
Urine Total Metanephrines (NORM+MET)	2789mcg/24hr	95-475mcg/24hr
Plasma Free Metanephrine (PMET)	44pg/ml	<=57 pg/ml
Plasma Free Normetanephrines (PNORM)	607pg/ml	<=148pg/ml
Plasma Free Total Metanephrines (PMET+PNORM)	651pg/ml	<=651pg/ml

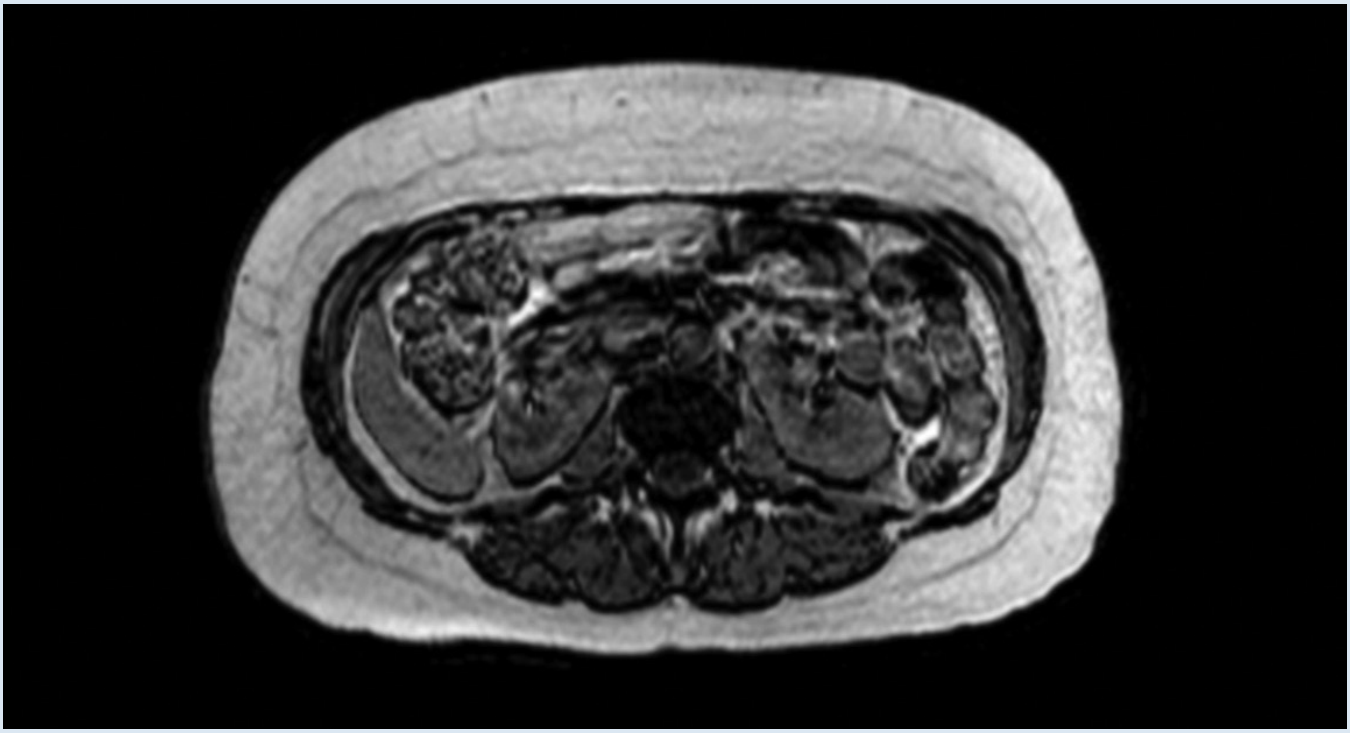

Figure 1: MRI of 2.3x2.7 centimeter rounded mass

lying anterior to the upper aspect of the left kidney was seen. The patient was referred for a Magnetic Resonance Imaging (MRI) study of her abdomen to further investigate this mass. The MRI (Figure 1) revealed a 2.3 x 2.7 centimeter rounded mass seen just above and anterior to the left kidney, suspected to be related to the left adrenal gland. (Figure 1)

Diagnosis

Urine NORE was five times above the upper limits of normal, urine EPI was only twice the upper limits of normal, but the urine total catecholamines were almost five times the upper limits of normal. The urine NORM level was seven times the upper limits of normal, urine MET was four times the upper limits of normal, while the urine total metanephrines were almost six times the upper limits of normal. The PMET value was within the normal range while the PNORM value was four times the reference range whereas the plasma free total metanephrines value is located at the upper limit of normal. All of the values except for the 24-hour urine Vanilylmandelic acid, urine EPI, PMET, and plasma free total metanephrines value were increased to three times above the normal limit which is indicative of pheochromocytoma. With both the supportive laboratory and radiology results, a diagnosis of pheochromocytoma was made.

Treatment

The patient was then referred to a surgeon who specialized in endocrine tumors. After being prepped with preoperative alpha-blockade, the patient underwent successful laparoscopic adrenalectomy and pathology showed a pheochromocytoma. Six-month follow-up of plasma metanephrines and abdominal MRI came back normal.

that the patient stop these medications for at least two weeks before testing. Specifically for the plasma metanephrine testing, the patient must stop the above medications, fast, stop acetaminophen 5 days before the test and have no caffeine the day of the test. Then, the patient must rest supine for 20 minutes and then their blood is drawn.[4]

When interpreting the values from either test, the clinician should be suspicious of pheochromocytoma when the values are increased 3 times above the normal limit.[1] Furthermore, abnormal results are plasma metanephrine levels above 96 pg/ml, normetanephrine above 130 pg/ml or total metanephrines above 200 pg/ml.[4] Clinician's should be cautious when performing this test on renal failure patients who are on hemodialysis because they will already have high levels of metanephrines and catecholamines.[2]

If the patient is on a medication or involved in an activity that would cause high levels, it is suggested the clinician perform a repeat test after the drugs have been tapered and discontinued for two weeks prior to the test. Another option is to perform a clonidine suppression test. Clonidine is a centrally acting α_2-adrenergic receptor agonist, which suppresses release of the catecholamines from the neurons but not in pheochromocytomas. The catecholamine and metanephrine levels are measured before and 3 hours after oral administration of 300 μg of clonidine. If the levels are high in both the before and after measurements, the presence of pheochromocytoma is confirmed. However, if the levels are lower after the administration of clonidine, the patient has essential hypertension. The clonidine suppression test is not recommended as a first line test, but it helps confirm the presence of pheochromocytoma. It is not recommended to perform a phentolamine or glucagon provocation test due to their low sensitivity.[1,2]

Another test that can be performed is Chromogranin A, which is seen in a wide spectrum of neuroendocrine tumors and therefore not very specific, but is increased in 80% of pheochromocytomas. Also, plasma neuropeptide Y is increased in 87% of pheochromocytomas, but it is not as accurate as the plasma or 24-hour urine fractionated metanephrines and catecholamines measurement.[2] Also, if the patient has metastasized pheochromocytoma, the most accurate biomarker is plasma methoxytyramine.[3]

After the biochemical evidence has been confirmed, the next step is tumor localization via Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) (sensitivity >95%, specificity >65%). It is recommended to do a CT and MRI of the adrenal glands (85% of pheochromocytomas are found here) and the abdomen and pelvis (95% are found here but are typically called paragangliomas).[2] The initial study, according to Mittendorf,[4] should be an abdomen and pelvis CT scan (unenhanced, contrast-enhanced, and delayed contrast-enhanced with 2-5 mm thick scanning sections). Next, should be an MRI, which is better than a CT at assessing the tumor and its relationship to the surrounding vessels. It can also help identify vascular invasion in case the tumor has metastasized.[4]

Another test to be performed is a chemical shift MRI, which is lipid-sensitive imaging. Pheochromocytomas have low lipid content, whereas, benign cortical adenomas have equal parts lipid to water, lose signal on out-of-phase images, but appear relatively bright on in-phase images. Overall, the general pattern of imaging for pheochromocytomas is as follows: enhancement with IV contrast medium on CT, high signal intensity on T2-weighted MRI, cystic and hemorrhagic changes, and they can be of variable size.[3] They are also known to be bilateral, mimic adrenal cysts, and have no signal loss on opposed-phase images.[2,4] The use of ultrasound isn't recommended except in pregnant women or if other structural issues are present that would affect the imaging.[3]

Another localization test that can be performed especially when biochemical evidence indicates the presence of a pheochromocytoma but it can't be found on MRI or CT, the test of choice is 123I-MIBG or 131I-MIBG Scintigraphy.[4] 123I-MIBG is preferred over 131I-MIBG because it allows for single-photon emission computed tomographic (SPECT) images.[2] 123I-MIBG is indicated when abdominal imaging is negative, in recurrent or metastatic cases, in people with distorted anatomy, and in tumors larger than 5cm.[4] 123I-MIBG or 131I-MIBG are radioactive tracers that accumulate in the tumor and can identify any pheochromocytoma regardless of location. Therefore, it has a greater specificity of 95-100% compared to MRI and CT (50%) but a lower sensitivity of 80%.[4] 123I-MIBG or 131I-MIBG testing should also be performed in a tumor larger than 10 cm because there is a greater risk for malignancy.[2]

Thyroid ablation must also be prevented by giving a saturated solution of potassium iodide (Lugol's solution) or potassium perchlorate before and after administration of the radioactive iodine.[2,4] Repeat scans may have to be performed for up to 72 hours for optimal imaging and it is best if they correlate with the CT and MRI scans.[4]

Other tests that can be performed include somatostatin receptor imaging with 111In-DPTA-pentetreotide, which has a low sensitivity, and positron emission topography (PET) with 18F-fluorodeoxyglucose (FDG) or 11C-hydroxyephedrine or 6-[18F]fluorodopamine.[1,2] Overall, the PET imaging is nonspecific and not widely used because it is really expensive and has a short half-life.[4] If all tests are negative, repeat noninvasive localization studies[3] and biochemical evaluations.

TREATMENT

The gold standard of treatment for pheochromocytoma is surgical excision. Removal not only eliminates the hypertension and the episodes but also prevents the patient from slipping into lethal hypertensive crisis if it isn't removed. If the patient has extensive disease, removal can prevent serious complications like urinary tract, cord compression or cardiac obstruction.[3]

Before the surgery and after all of the biochemical evidence and tumor localization studies have been performed, the patient must undergo a very important pre-operation process. First, the patient undergoes an alpha blockade, which lasts seven to ten days to normalize the blood pressure, control arrhythmias, and expand the contracted blood volume.[2]

The main goal of the blockade is to maintain the blood pressure below 160/90 mmHg according to Neuman[1] but Bope and Kellerman[3] uses stricter criteria: 140/90 mmHg for 24 hours and orthostatic hypotension can be present but not below 80/45 mmHg. Williams[2] suggests monitoring the blood pressure seated and standing twice a day and using even stricter controls of 120/80 mmHg (seated) with a systolic blood pressure over 90 mmHg standing. However, the blood pressure can be modified based on age and other comorbidities. Start the patient on an alpha-adrenergic agonist (typically phenoxybenzamine) on a low-dose (5-10 mg orally, one to three times a day) and increase the dose by 10-20 mg every two to three days as tolerated.[1,2] The final dose shouldn't exceed 20-30 mg phenoxybenzamine three times a day[1] or 2mg/kg/day according to Mittendorf.[4] The blockade might have a longer duration for those who have a catecholamine cardiomyopathy, catecholamine-induced vasculitis, or a recent MI.[2] While awaiting the blockade, the patient can be given oral prazosin or IV phentolamine to help manage the paroxysms.[1] Common side effects with an alpha blockade are orthostasis, nasal congestion, and marked fatigue.[2] If long-term management is needed like in cases of malignant pheochromocytoma, α1-blockers (prazosin, terazosin, doxazosin) because the side effects, are not as severe and typically the alpha blockade is incomplete. However, they do help preserve the α2 catecholamine reuptake mechanism.[2,4]

On day 2 or 3 of the blockade, add plentiful amounts of salt intake and hydration to avoid orthostasis and because of the catecholamine-induced volume contraction.[1,2] After the patient is sufficiently alpha-blocked (normally two to three days), a beta-blocker is added especially if tachycardia persists. It is very important the patient be sufficiently alpha blocked before the beta blocker is started to avoid hypertensive crisis due to inhibition of the β2-adrenoreceptor mediated vasodilation in the presence of catecholamine stimulation.[3] The preferred beta-blockers are atenolol, esmolol, and metoprolol because they are cardioselective and don't cause as many side effects. Start the patient on a low dose (10 mg every six hours to start) and if it is tolerated then convert to a long-acting beta agonist on day 2. It can also be increased as necessary to control the heart between 60-80 beats per minute. The clinician must be cautious giving a patient who has asthma or congestive heart failure a beta-blocker because chronic catecholamine excess can lead to a myocardiopathy or acute pulmonary edema.[2]

Other medications that can be added to help control blood pressure when alpha and beta agonists are not sufficient are calcium channel blockers or angiotensin-converting-enzyme (ACE) inhibitors.[1] Their main role is to supplement the combined alpha and beta blockade when blood pressure control is inadequate or for patients with bad side effects on the other blockades. The final resort is to add a catecholamine synthesis inhibitor (metyrosine) when other agents are not effective or if tumor manipulation or destruction is increased or you a calcium channel blocker is contraindicated.[2]

If the patient does go into acute hypertensive crisis, the best medication to use is IV sodium nitroprusside because it has a rapid onset and a short half-life/duration. The dosage is 0.5-5.0 μg/kg of body weight per min and is adjusted every few minutes to achieve the target blood pressure response. Do not titrate any higher than 3 μg/kg of body weight per min. Another drug that can be use is phentolamine, which is a short-acting nonselective alpha-blocker available in lyophilized form in 5-mg vials. Initially, a test dose of 1 mg is given and followed by repeat 5 mg boluses or via continuous infusion. The response peaks in two to three minutes after a bolus injection and lasts 10-15 minutes. The last drug that can be used is nicardipine at an infusion rate of 5 mg/hour and titrated for blood pressure control. The rate can increase to 2.5 mg/hour every 15 minutes up to a maximum of 15.0 mg/hour for proper control.[2] A calcium channel blocker can also be added at a dose of 750 mg every 6 hours.[4]

One final item that can be given pre-operatively is vaccines against strep pneumonia, haemophilus influenza, and Neisseria meningitides. These are very important especially if the patient is going to have a splenectomy for a large left adrenal pheochromocytoma.[3]

The preferred technique is an atraumatic endoscopic (more specifically laparoscopic) surgery using a transperitoneal or a retroperitoneal approach. It offers fewer complications, a faster recovery and optimal cosmetic results over a laparotomy.[1] More specifically, the retrotransperitoneal approach is feasible, safe, faster and less painful.[4] If the patient has a solitary intra-adrenal pheochromocytoma, the treatment of choice is a laparoscopic approach for tumors smaller than 8

cm in diameter according to Williams[2] and 6cm according to Mittendorf.[4] It offers a faster resolution of post-operative ileus, decreased analgesic requirements, shorter hospital stay, and shorter convalescence with a quicker return to normal activity.[4]

On the morning of the surgery, give alpha and beta blockers early. For anesthesia, Williams[2] recommends using IV propofol, etomidate or barbiturates in combination with synthetic opioids. Avoid desflurane and halothane gases but other gases are fine to use. It is prudent to avoid fentanyl, ketamine, and morphine because it can cause catecholamine release and avoid atropine because it can cause tachycardia. During the surgery, monitor heart rhythm and cardiovascular and hemodynamic variables intra-arterial pressure.[2] The blood pressure can fluctuate during surgery. For hypotension use volume infusions and for hypertensive crisis use a nitroprusside infusion.[1] If the patient also has congestive heart failure or decreased cardiac reserve, it is important to monitor pulmonary capillary wedge pressure.[2]

When the tumor is greater than 6 cm, there is a higher risk for malignancy, and it is recommended to employ an open adrenalectomy because it is typically a difficult dissection, invasive, adhesions, or if the surgeon is inexperienced.[2,4] Try to remove all of the pheochromocytoma and as much as possible of the malignant tumor.[2] An "unresectable" cardiac pheochromocytoma may require a cardiac transplant.

Familial disease can present in a variety of ways. If there is a unilateral tumor and a normal contralateral gland, perform a total laparoscopic total adrenalectomy. However, familial disease most often presents bilaterally and the surgeon should plan to do a bilateral adrenalectomy to remove both glands.[2,4] The bilateral adrenalectomy is performed to prevent contralateral disease and eliminates the risk of catecholamine crisis and distant metastases. For this procedure, give the patient glucocorticoid stress coverage while being transferred to the operating room and initiate treatment in the operating room if an unexpected bilateral adrenalectomy is initiated.[2] An unfortunate result of this procedure however, is the need for lifelong steroid hormone replacement therapy and an increased risk of adrenal insufficiency.

Another technique that can be used in familial cases, which may prevent the need for chronic corticosteroid replacement and minimizes risk for adrenal insufficiency is a unilateral cortical-sparing procedure with removal of the entire contralateral gland while the remaining cortex is left in situ. Preserving one side reduces risk of recurrent disease.[4] The risk for metastases and malignancy is very unlikely in inherited syndromes as is the risk for recurrent disease.[4]

Some unlikely events that can happen during surgery are the ligation of the adrenal vein, which can cause abrupt cessation of catecholamine release and can lead to acute hypotension. It is important to have central and peripheral venous access, a radial artery catheter and some get a pulmonary artery catheter. Treat the hypotension with epinephrine and norepinephrine.[4] Hypotension may also occur during the surgery and should be treated with fluids and colloids and then intravenous pressor agents if needed.[2]

After the surgery, give fluids with 5% dextrose to avoid hypoglycemia and make sure to monitor glucose levels, which can decrease from less production and increased utilization in the absence of catecholamine excess and persistence of alpha blockers.[2,3] Hypotension doesn't occur as often if the patient is treated pre-operatively with the blockades and volume expansion.[2] If the patient is hypotensive, exclude hemorrhage first, but the most likely reason for the hypotension is the prolonged effects of the alpha-blockers in the presence of reduced catecholamine levels. Avoid vasopressor agents when treating hypotension when long-acting beta-agonists or metyrosine have been used because they paralyze the vascular bed in a dilated state; therefore the treatment of choice is volume replacement.[3] The most common adverse event is sustained hypertension which can last anywhere from 4-8 weeks or it can be permanent.[2] Hypertension in the first 24 hours is attributed to pain, volume overload, or autonomic instability; treat symptomatically.[3]

At about 5-7 days post-surgery, take a urinary specimen to make sure increases due to the surgery have dissipated.[3] Within 1-2 weeks after surgery, perform a 24-hour urinary fractionated catecholamines and metanephrines measurement and check annually for life. If the levels are normal, it means a complete resection was performed while increased levels indicate residual tumor and follow up CT or MRI is needed.[2] Make sure to document catecholamine normalization and perform an adrenocorticotropic hormone test to exclude cortisol deficiency when a bilateral adrenal cortex-sparing surgery is performed.[1] If a bilateral adrenalectomy was performed, consider adrenocortical insufficiency (subsequent risk of acute adrenal insufficiency occurs in 25-33% of patients) and prescribe lifelong glucocorticoid and mineralcorticoid replacement therapy.[2,4] Recurrence rates are highest for those with familial disease right-sided adrenal pheochromocytoma.[2]

The most dangerous complication that can occur is hypertensive crisis, which manifests as a severe headache, visual disturbances, acute myocardial infarction, congestive heart failure or cerebrovascular accident. Treat with an intravenous bolus of phentolamine (5 mg) and repeat every 2 minutes or as a continuous infusion until the hypertension

is under control. Another treatment that can be used is a continuous infusion of sodium nitroprusside (Nitropress) or oral or sublingual nifedipine (Procardia).[3]

MALIGNANT PHEOCHROMOCYTOMA

About 10% of pheochromocytoma cases are malignant. It is very hard to diagnose malignant pheochromocytoma because histological criteria of cellular atypia, presence of mitosis, and invasion of vessels or adjacent tissues don't reliably identify the tumors that metastasize.[1] Therefore malignant pheochromocytomas are identified by the presence of distant metastases (sites where chromaffin cells are normally absent).[1,3] These are most commonly found in the lungs, bone (spine skull and ribs), and liver (vascular pathway of spread).[1, 4] It can also metastasize hematogenously or via lymphatic routes.[3] Larger tumors, higher urinary metanephrine levels (especially methoxytyramine), and a shorter duration of presenting symptoms also indicate malignancy.[3,4] Methoxytyramine can be used as a surrogate biomarker to assess tumor burden, disease progression, and treatment response in malignant pheochromocytomas.[3]

Half of the metastatic pheochromocytomas are found at the original presentation and the other half develop at a median interval of 5.6 years but can be delayed up to 24 years. Half of these patients get an indolent form and live for 20 years while the other half develop a rapidly progressive form and die in 1-3 years.[2] Overall, the 10-year survival rate is 40% according to the Mittendorf[4] while Williams[2] suggests the 5-year survival to be less than 50%. Furthermore, Neuman[1] proposes a 5-year survival of 30-60%[1] while Bope and Kellerman[3] suggest the 5-year survival after the diagnosis of the first metastases to be 67%.

Therapy should be targeted towards the aggressiveness of the tumor behavior.[2] Overall, treatment is very challenging. The main techniques employed include tumor mass reduction, alpha-blockers for symptoms, chemotherapy, and 131I-MIBG radiotherapy treatment.[1] Surgery can be curative but if the tumor is extensive, it is likely the tumor will re-grow locally.[4] If possible, Williams[2] suggests resecting the metastases, but it is highly dependent upon their location. Skeletal lesions that are painful or threaten structural function are typically treated with external radiotherapy, cryoablation or surgically. For large, unresectable liver metastases, Williams[2] recommends using thrombotic therapy while small liver metastases get radiofrequency ablation. Ablative therapy is preformed with extreme caution because of the risk for massive catecholamine release. For this reason, the patient must get blockades plus metyrosine before the procedure. For unresectable soft tissue lesions external radiotherapy is used.[2]

If the tumor is aggressive, all sources agree that chemotherapy is the next step. Neuman[1] and Williams[2] suggest using Averbuch's (CVD) protocol, which consists of dacarbazine (600mg/m2 on days 1 and 2), cyclophosphamide (750 mg/m2 per body surface area on day 1) and vincristine (1.4 mg/m2 on day 1) repeated every 21 days for 3-6 cycles, and nuclear medicine therapy. Chemotherapy palliation or complete and partial responses are achieved in about half or 57% (median duration = 21 months, range 7 to greater than 34).[1,2] Complete and partial biochemical responses are seen in 79% (median duration >22 months, range 6 to >35 months). All patients had an objective improvement in performance status and blood pressure. Continue the CVD protocol until new lesions develops or there is an increase in tumor sites.[2] The patient must be blockaded the whole time to prevent massive catecholamine release. It is also suggested the first cycle be done in hospital under close observation.[2]

An alternative to chemotherapy is 131I-MIBG treatment using 200-mCi doses at monthly intervals over 3-6 cycles.[1] Mittendorf[4] argues it should be the first if an operation can't be performed because it is a well-tolerated treatment and improves the quality of life of the patient . He also suggests using a single dose (3.7 – 9.1 GBq) intravenously over 2-3 hours, cumulating in a dose of 85.9 GBq for 3-6 months. Williams[2] claims this treatment gives partial or temporary responses in a third of patients. Mittendorf[4] also concludes that hormonal responses occur in 45% of patients and tumor responses in 30%. Other studies suggest the role of tyrosine kinase inhibitors in the treatment for metastatic pheochromocytomas.[2] A combination therapy can also help increase the uptake of 131I-MIBG because it has additive effects. Finally, recent studies suggest that VEGF expression is higher in metastatic pheochromocytomas. A proposed treatment role is to employ anti-VEGF monoclonal antibodies, which inhibits angiogenesis and hopefully stops tumor spread.[4]

PREGNANCY

Pheochromocytoma is an unusual development in pregnant women however it can cause the death of the mother and fetus.[2] Biochemical testing is the same as in non-pregnant women but the preferred imaging modality is MRI without gadolinium enhancement. 123I-MIBG and CT are contraindicated. Pre-operative preparation is the same and so is the treatment for hypertensive crises except for avoiding nitroprusside.[2] A quick removal is suggested if the woman is in the first or second trimester of pregnancy while an endoscopic removal is recommended at 4-6 months of gestation. It is very possible that the surgery can be followed by an uneventful childbirth.[1] If the woman is in the third trimester, a cesarian section and

tumor removal at the same time is recommended. It is also important to avoid spontaneous labor and delivery. Depending on the location of the tumor, the treatment protocol might have to be modified.[2] Neuman[1] suggests screening families who have a history of pheochromocytomas especially in women of reproductive age.

DISCUSSION

Pheochromocytoma is a relatively uncommon, normally benign tumor and is associated with hypertension, episodes of headaches, palpitations, and diaphoresis. In our patient, she initially presented with the "classic triad" of symptoms and hypertension. She was concerned because her palpitations were becoming progressively worse even with over the counter medications that seemed to control her episodes for a short while. Even though multiple primary care physicians and cardiologists who diagnosed her with atrial fibrillation were treating her, her palpitations were becoming worse which is why she still sought out treatment from our primary care office.

With the patient's history and clinical presentation, this led the physician to further investigate other non-cardiac causes. Most patients with pheochromocytoma present in the fourth or fifth decade and it equally affects men and women. However, many hereditary syndromes will present with pheochromocytoma in childhood or the second decade. Thus, a thorough family history can help lend support for the diagnosis.

In patients suspected of having pheochromocytoma, the full work-up includes: (1) a thorough history and physical exam, (2) a 24-hour urine or plasma free metanephrine and catecholamine analysis, and (3) a CT and MRI. If the biochemical and radiological evidence doesn't match, consider performing a repeat test or a 131I-MIBG Scintigraphy. Since most of the values from the patient's 24-hour urine and plasma free catecholamine and metanephrine analysis are increased to three times above the normal limit and a mass was found on MRI, a diagnosis of pheochromocytoma was made. The patient was sent to a surgeon who specialized in endocrine tumors and underwent a laparoscopic adrenalectomy and was pre-operatively alpha blockaded.

The episodic complaints of headaches, palpitations, and diaphoresis are explained by the massive release of catecholamines from the tumor, which can be caused by a number of things including: positional changes, chronic volume depletion, medications, and etc. This diagnosis also further accounts for the nonspecific signs of pheochromocytoma including CREST syndrome and her hyperlipidemia.

With the tumor excised, these symptoms are alleviated and typically no further treatment is necessary. In cases of malignant pheochromocytoma, chemotherapy or radiation are both used to combat the disorder, which is typically present at diagnosis. It is advised that the patient be evaluated yearly by 24-hour urine or plasma free catecholamine and metanephrine collection to check for recurrence.

CONCLUSION

In summary, a typical case of Pheochromocytoma was presented but it somehow eluded the detection by multiple other primary care physicians and cardiologists. Luckily, the tumor was caught and properly excised before the patient fell into hypertensive crisis. Since pheochromocytoma is rare and known as the "great masquerader,"[1] it is important to thoroughly evaluate patients with seemingly common recurrent medical complaints especially if the patient feels they are getting worse.

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