Lesson 283: PreAnesthetic Assessment of the Patient With von Hippel-Lindau Syndrome

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Needs statement

Anesthesiologists are trained to appreciate and respond appropriately to the considerable consequences of pheochromocytomas. It is, however, less appreciated that the tumors also may be associated with other syndromes that pose significant risk for patients undergoing anesthesia.
Learning Objectives

At the end of this activity, the participant should be able to:

1. Cite the perioperative mortality rate for diagnosed pheochromocytoma.
2. Describe the pathophysiology of pheochromocytoma.
3. Discuss the association between pheochromocytoma and other syndromes.
4. Identify the “rule of 10s.”
5. Present an anesthetic plan for patients with von Hippel-Lindau syndrome (vHLS).
6. List the 3 familial syndromes of multiple endocrine neoplasia (MEN).
7. Describe the characteristics of vHLS.
8. Identify appropriate laboratory studies to diagnose pheochromocytoma.
9. Estimate the age-related prevalence of adrenal incidentalomas.
10. Manage the postanesthetic care of a patient with vHLS.

Case History

A 23-year-old man whose medical history was significant for vHLS presented for a laparoscopic right partial nephrectomy. The patient was diagnosed with renal cell carcinoma, found incidentally on a computed tomography (CT) scan to assess for rib fractures after a motor vehicle accident. The patient’s surgical history was significant for a craniotomy with tumor resection (9 years earlier) secondary to hemangiomas related to vHLS, and a right total adrenalectomy and left partial adrenalectomy (8 years earlier) to remove pheochromocytomas. Other than the renal cell carcinoma, no other lesions secondary to vHLS had recurred. The patient—183 cm tall, weighing 100 kg, with blood pressure of 125/78 mm Hg, and heart rate of 80 beats per minute—was taking medication that included a muscle relaxant for the treatment of back spasms after the accident. He was otherwise asymptomatic.

Pheochromocytoma is one of the more challenging medical conditions faced by the anesthesiologist. The paroxysmal hypertensive crises and cardiac manifestations (including sinus tachycardia, bradycardia, and arrhythmias) which are the hallmarks of the condition require the highest degree of vigilance. Management of pheochromocytoma has significantly advanced since the first surgical reports appeared in the 1920s. Today, the mortality rate is less than 5%.1

Among patients diagnosed with hypertension, roughly 0.1% of cases are attributable to pheochromocytomas2—a small but not insignificant statistic given the high incidence of hypertension. These patients have a medical condition that, in most instances, can be cured if diagnosed and treated correctly. However, patients who remain undiagnosed are at risk for further morbidity and high mortality, particularly if they undergo a surgical procedure. Between 25% and 50% of patients with undiagnosed pheochromocytomas die of complications during induction of anesthesia or intraoperatively during procedures for other medical conditions.3

Pheochromocytomas are very vascular tumors comprised of chromaffin tissue, which secretes epinephrine and norepinephrine. These tumors are most commonly found in the adrenal medulla, but can be found anywhere chromaffin cells reside within or close to sympathetic ganglia, including the spleen, broad ligament, bladder, right atrium, and bifurcation of the aorta.3 While isolated pheochromocytomas of a nonfamilial etiology comprise most cases, it is important to understand the
hazards associated with pheochromocytomas in more complex clinical settings. Approximately 5% of pheochromocytomas are associated with another disorder such as von Hippel-Lindau syndrome (vHLS). The current case is one example of many atypical contexts in which pheochromocytomas arise.

Incidence and Epidemiology

The highest incidence of pheochromocytoma occurs in the fourth and fifth decades of life. In adults, approximately 80% of tumors are solitary and unilateral, developing in one adrenal gland. The remaining 20% of tumors are categorized as bilateral lesions or extra-adrenal masses. The rule of 10s refers to data indicating that 10% of the tumors are extra-adrenal, 10% are bilateral, and 10% are malignant. Typically, malignant tumors spread to the liver via lymphatics and venous routes; recurrence is estimated to be 8%. Five percent of pheochromocytomas are inherited, as either an isolated phenomenon or part of a familial syndrome.

Symptoms

Release of catecholamines from pheochromocytomas accounts for most symptoms, usually headaches, palpitations, and sweating. Both epinephrine and norepinephrine are synthesized in, stored in, and secreted from, pheochromocytomas. The majority of pheochromocytomas release both epinephrine and norepinephrine. However, some tumors contain and secrete only 1 of the catecholamines. Epinephrine-secreting tumors produce palpitations, sweating, heat intolerance, tremulousness, pallor and flushing, headache, and weight loss. With the potential for very strong β-stimulation, these tumors can infrequently cause severe hypotension or shock. Characteristically, norepinephrine-secreting tumors are associated with more benign symptoms and can be misdiagnosed as essential hypertension.

Tumors that secrete both catecholamines exert a wide spectrum of effects. Few patients are asymptomatic. Approximately 50% of patients experience nonparoxysmal hypertension, which is either sustained or labile. The remainder experience paroxysmal elevations in blood pressure with the worst symptoms associated with the greatest fluctuations in plasma catecholamine levels. The frequency of symptoms varies. Patients may live for years without a recurrent attack, whereas others experience more than 20 sudden-onset attacks daily. Most attacks last a few minutes to a few hours, but some may be as short as several seconds and others may persist for days.

In addition to causing hypertension, pheochromocytomas can lead to deleterious but less common cardiac manifestations. Sinus tachycardia, sinus bradycardia, supraventricular dysrhythmias, and premature ventricular contractions have been reported. Patients without a history of coronary artery disease may suffer anginal pain and myocardial infarctions that are believed to be the result of catecholamine-induced coronary artery spasm. Electrocardiographic changes include right and left bundle branch blocks, nonspecific changes to the ST segment and T wave, and prominent U waves.

Catecholamine cardiomyopathies are rare and presumably associated with a longer duration of disease and exposure to catecholamines. These cardiomyopathies can lead to heart failure and death, albeit rarely. The mechanism has not been fully elucidated but persistent hypertension can cause a hypertrophic cardiomyopathy. Dilated cardiomyopathies are less common.

Other findings may include weight loss, carbohydrate intolerance due to decreased insulin production, and increased hepatic glucose production. Orthostatic hypotension may be seen in as many as 70% of
patients. The exact mechanism is unknown but may involve desensitized \(\alpha\)-adrenergic receptors, sympathetic reflexes from the increased amount of circulating catecholamines, or volume depletion related to hypertension.\(^4\) Patients with pheochromocytomas in the bladder wall may develop hematuria and bladder spasms with polyuria.

**Diagnosis and Laboratory Findings**

The first step in diagnosis is often the measurement of 24-hour urinary metanephrine and vanillylmandelic acid, and plasma catecholamines. No test is perfect, with each having a different degree of sensitivity and specificity. The sensitivity of a test for plasma-free metanephrine is approximately 96% to 100%; the specificity is lower, from 82% to 96%. In comparison, testing for urinary metanephrine and catecholamines has a specificity of 98% and a sensitivity of 90%.\(^5\) Any of the results for biochemical markers can be negative despite positive clinical findings and the presence of a tumor.

Conversely, use of several drugs can lead to false-positive results for catecholamines and metanephrine, wrongly suggesting a diagnosis of pheochromocytoma. The list includes antipsychotics, L-3,4-dihydroxyphenylalanine (L-dopa), tricyclic antidepressants, clonidine, phenoxybenzamine, caffeic acid (found in decaffeinated coffee), ethanol, and acetaminophen. Additionally, substantial physical stress can result in false-positive test results.\(^5\)

The clonidine suppression test can be used to rule out a rise in catecholamines from other causes.\(^6\) Because a pheochromocytoma secretes catecholamines that are independent of neurogenic control, the administration of clonidine will not result in suppression. Imaging studies that include a computed tomography (CT) scan, magnetic resonance imaging (MRI), and a metaiodobenzylguanidine (MIBG) scintiscan should be conducted to confirm a diagnosis. CT and MRI are comparable in sensitivity (98% and 100%, respectively), but both have lower specificities (CT, 70%; MRI, 67%). An MIBG scintiscan has a specificity of 100%, but a lower sensitivity of 78%.\(^7\) All components of an evaluation must be taken into account to arrive at the correct diagnosis.

**Familial Pheochromocytomas in Association With Syndromes**

Five percent of pheochromocytomas are of familial origin, passed down as an autosomal dominant trait and found in isolation or in association with a syndrome—including vHLS, multiple endocrine neoplasia (MEN) type 2A or 2B, and von Recklinghausen neurofibromatosis. Pheochromocytoma is generally the most threatening component of vHLS and MEN 2A/2B.\(^8,9\) Patients with any of these syndromes should be evaluated preoperatively for pheochromocytoma regardless of medical history and whether or not they show any signs or symptoms of catecholamine-secreting tumors.
vHLS is an autosomal dominant condition with variable expression and incomplete penetrance (Figure). The disease was first characterized more than 100 years ago when Eugen von Hippel described angiomas of the eye, in 1904; then Arvid Lindau described angiomas of the cerebellum and spine in 1927. Findings in patients with vHLS include capillary hemangioblastomas of the retina (60%-70% of patients) and hemangioblastomas of the central nervous system (CNS; 30%-70% of patients). Most CNS lesions are found in the cerebellum. Less commonly seen are erythrocytosis, pancreatic and renal cysts, renal cell carcinoma, and hypernephroma. Pheochromocytomas occur in about 10% to 20% of vHLS patients and are more likely to be bilateral, with a tendency to recur after surgical removal.

The age that a patient receives a diagnosis of vHLS may vary greatly, with the average age being 26 years. This leads to an earlier age that pheochromocytoma may be diagnosed in these patients, compared with those in whom pheochromocytoma is not associated with another disorder.

The syndrome is characterized by a mutation in the tumor suppressor gene on chromosome 3p25.3. As long as one copy of the VHL gene is producing functional VHL protein in each cell, tumors do not develop. If a mutation occurs in the second copy of the VHL gene during an individual’s life, the cell has no working copies of the gene and produces no functional VHL protein. A lack of this protein causes tumors characteristic of vHLS to develop.

Because both alleles must be mutated for the disorder to develop, it would be reasonable to conclude that the mutation is recessive. However, based on patterns of heredity, vHLS is—paradoxically—an autosomal dominant disorder; individuals who have already inherited one mutated copy of the gene...
have an extremely high probability of developing the second mutation. An inherited mutation of the VHL gene is responsible for about 80% of cases. In about 20% of cases, however, the altered gene is the result of a new mutation that occurs during the formation of reproductive cells (eggs or sperm) or early in fetal development. This is quite rare because the probability is small of a mutation occurring in a cell in which both alleles are previously normal. Also, the first mutation must be followed by a second for the syndrome to develop.

A patient might receive a diagnosis of vHLS when an associated disease is causing symptoms. Angiomatosis, hemangioblastomas, pheochromocytoma, renal cell carcinoma, pancreatic cysts, and café au lait spots are all conditions associated with vHLS. For example, angiomatosis develops in 37.2% of patients with vHLS—usually in the retina; however, other organs can be affected. As a result, loss of vision is very common in these patients. An average of 10% to 20% of patients with vHLS also develop pheochromocytomas. The risk for these tumors—which are, histologically, usually benign—appears to hinge on the precise nature of the mutation responsible for vHLS in a specific family. In kindreds with vHLS who demonstrate a deletion or protein-truncating mutation of the VHL gene (type 1 vHLS), the risk for pheochromocytoma is less than 10%. In contrast, the risk for pheochromocytoma is approximately 50% in kindreds with a missense mutation (type 2 vHLS).

The age of onset of the disease varies widely, as does the organ system affected and severity of the effect, which suggests that the second mutation can occur in different types of cells and at various times in an individual’s life. If a patient with vHLS has coexisting lesions or disorders that require surgical correction in addition to the removal of a pheochromocytoma, the resection of the pheochromocytoma should often be assigned the higher priority. Patients with CNS lesions may have complications. If the intracranial mass is addressed first, the anesthesiologist is faced with a patient with potential for extreme hypertension leading to intracranial bleeding perioperatively. If the decision is made to resect the pheochromocytoma first, vasodilators required for controlling hypertension may increase cerebral blood flow and intracranial pressure—which may be offset initially by hyperventilation, placement of an intraventricular drain, or administration of mannitol and/or furosemide. This dilemma must be discussed with the operative team to decide which procedure should take precedence.

MEN comprises 3 different familial syndromes inherited as autosomal dominant traits. The profile of MEN type 1 does not include pheochromocytoma and therefore does not pertain to this case. MEN type 2A (Sipple syndrome) includes medullary thyroid cancer (97%), pheochromocytoma (50%), and hyperparathyroidism (20%); it is more similar to vHLS regarding the presentation of pheochromocytoma. MEN type 2B—which is rarer than 2A—is associated with medullary thyroid cancer, pheochromocytoma, marfanoid body habitus, and mucosal neuronal syndrome with mucosal neuromas and intestinal ganglioneuromas. Also, in patients with MEN type 2B, tumors generally appear later in life and are rarely malignant or bilateral.

In patients with MEN type 2A, calcium levels must be checked if the pheochromocytoma is resected before removal of the parathyroid glands because most of these patients have asymptomatic hypercalcemia. Symptomatic patients may experience fatigue, weakness in general or proximal muscle weakness, confusion, polyuria, and polydipsia. Patients also may have hyporeflexia, pseudogout, anemia, subperiosteal bone resorption, and renal stones. Abnormal electrocardiograms include shortened Q-T intervals and prolonged P-R intervals.
Cardiac dysrhythmia is the most important potential complication of hypercalcemia. Q-T intervals do not necessarily correlate with changes in calcium concentrations; therefore, blood gases must be analyzed in conjunction with blood calcium levels. The management of hypercalcemia includes the administration of sodium-containing IV fluids along with a loop diuretic (furosemide), which causes dilution of calcium and inhibits its renal reabsorption. Urine output must be closely monitored to assess renal dysfunction.

Other concerns for the anesthesiologist include muscle relaxant dosing, patient positioning, and the potential for airway compromise. The effects of muscle relaxants can be enhanced by hypercalcemia. A preoperative assessment of muscle weakness must be documented to record baseline values and tailor the administration of muscle relaxants to patients’ requirements. Careful positioning of the patient with appropriate padding is important to avoid pathologic fractures from osteoporosis. Although bilateral tumors frequently are found with medullary thyroid cancer, the tumors are rarely large enough to compress the airway. Airway compromise must be considered, however, and a difficult airway cart made available.

For any patient with vHLS or MEN type 2A or 2B presenting for surgery, pheochromocytoma should be suspected even if the patient is asymptomatic. Additionally, patients who have had a previously resected pheochromocytoma and are returning for surgery should be screened for a recurrence and for pheochromocytoma on the unresected side.

**Asymptomatic Pheochromocytoma**

A subset in pheochromocytoma classification is adrenal incidentalomas, which are clinically silent. These tumors likely contribute substantially to the statistic of 50% of pheochromocytomas being discovered postmortem. With advancements in imaging, the prevalence of these lesions is estimated at almost 3% in middle age to nearly 10% in the elderly. These pheochromocytomas may be hormonally active or inactive and, therefore, may not be detected during screening. Although incidentalomas may secrete catecholamines at a level at which the patient is asymptomatic, the lesions are not benign. Increasingly, the trend is to treat these subclinical tumors, given the possible association with increased morbidity.

When an undiagnosed pheochromocytoma is suspected intraoperatively during surgery for another condition, the consequences can be devastating. The mortality rate is as high as 80% during anesthesia. Any hypertensive patient not taking antihypertensive medications, and who presents for surgery with orthostatic hypotension, should be tested for pheochromocytoma. As many as 10% of cases of orthostatic hypotension may be due to pheochromocytomas. Additionally, any patient admitted for surgery to remove an adrenal mass must be evaluated for pheochromocytoma.

**Preoperative Management**

A key to avoiding intraoperative complications when removing a pheochromocytoma is to ensure optimal preoperative preparation. The most important goal is achieving control of blood pressure before surgery. The α-adrenergic receptor blocker, phenoxybenzamine, is a first-line therapeutic agent. Phenoxybenzamine is a nonselective α-blocker, targeting both α1 and α2 receptors; blockade is non-competitive and irreversible.
The patient can be started on phenoxybenzamine as an outpatient at least 2 weeks before the scheduled surgery to allow for maximal $\alpha$-receptor blockade and restoration of blood volume, given that chronic a-constriction causes volume depletion. The protocol for preoperative $\alpha$-receptor blockade generally requires 20 mg per day of phenoxybenzamine initially, followed by a gradual increase of an average of 40 to 80 mg per day—although the ultimate dose may be as high as 200 mg per day. Postural hypotension is the most common side effect. Although this relatively simple intervention cannot guarantee that intraoperative fluctuations in blood pressure will be prevented, it has been estimated to reduce perioperative mortality from 45% to 3%.6

Patients without cardiovascular symptoms despite the diagnosis of pheochromocytoma also may benefit from $\alpha$-receptor blockade. Apparent hemodynamic stability preoperatively does not preclude severe hemodynamic fluctuations intraoperatively—including increased systemic vascular resistance after induction of anesthesia, and hypotension after tumor resection. Calcium channel blockers have benefited patients who are normotensive generally but have paroxysmal hypertension.8 The advantage of calcium channel blockers is that they do not cause orthostatic hypotension; however, $\alpha$-receptor blockade is still the preferred therapy preoperatively.

Preoperatively, $\beta$ blockade is the second component of preparation if the patient has tachycardia, arrhythmias, or a history of coronary artery disease. $\alpha$-Adrenergic blockade must be established before $\beta$ blockade. If $\beta$-blocking agents are administered first, unopposed $\alpha$ blockade and, consequently, vasoconstriction could lead to a lethal—threatening hypertensive crisis. To optimize the patient for surgery, it is highly recommended that the Roizen criteria for sufficient $\alpha$ blockade are met (Table 1).28

Echocardiography should be performed preoperatively to assess catecholamine-related cardiomyopathy. In patients with cardiomyopathy, a longer period of preoperative preparation, while not always practical (as long as 6 months of treatment with $\alpha$ blockade has been suggested), may help reverse myocardial dysfunction.29 Untreated, a heart stressed by high levels of circulating catecholamines and arterial hypertension may not compensate for postoperative hypotension due to catecholamine withdrawal.

### Table 1. Roizen’s Criteria for Appropriate Preoperative $\alpha$ Blockade and Surgical Optimization

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<th>Criteria</th>
<th>Description</th>
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<tr>
<td>No in-hospital presurgical blood pressures measuring higher than 165/90 mm Hg at 24 hours before surgery</td>
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<tr>
<td>No orthostatic hypotension with blood pressure measuring lower than 80/45 mm Hg</td>
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<tr>
<td>Norelectrocardiogram showing ST-T changes 1 week before surgery</td>
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<td>No more than 1 premature ventricular contraction every 5 minutes</td>
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**Intraoperative Management**

Surgical resection of pheochromocytoma cures 90% of patients. Laparoscopic removal of pheochromocytomas is increasingly common, provided there is no local invasion and the mass is less than 6 cm. Large, recurrent, or invasive pheochromocytomas should be removed by laparotomy.31 Although the laparoscopic approach results in a shorter recovery time, overall survival rates are equal
with laparoscopic and open approaches. Neither approach has been proven superior regarding anesthetic management.

Intraoperatively, the greatest concern is release of catecholamines leading to life-threatening hypertension. Hypertensive crises can cause myocardial infarction, heart failure, dysrhythmias, and cerebral hemorrhage. Severe hypertension can occur at any time throughout surgery; however, induction, intubation, and tumor palpation tend to be the times of greatest catecholamine release.

Premedication with an anxiolytic, such as midazolam, decreases the stress response activating the sympathetic nervous system. After the patient has been admitted to the operating room and American Society of Anesthesiologists (ASA) standard monitors have been placed, it is desirable to obtain IV access—preferably at 2 reliable sites. Arterial cannulation is necessary and should be in place before anesthesia induction. The use of central venous monitoring and pulmonary artery catheterization depends on the clinical condition; they should be used in cases of cardiomyopathy, and cardiac compromise should be documented preoperatively.

Induction agents should be titrated slowly to maintain normotension. A short-acting opioid, such as fentanyl which is associated with minimal myocardial depression, in combination with a sedative-hypnotic is preferable to a sedative-hypnotic agent alone. Achieving an adequate depth of sedation is important so that the patient does not respond to the stimulus of intubation. Vecuronium or rocuronium may be used for muscle relaxation because these agents have few, if any, cardiovascular effects. Pancuronium should be avoided because of its sympathomimetic effects. Histamine release caused by atracurium can increase catecholamine release. Succinylcholine theoretically should be avoided because of possible potentiation of catecholamine release from contracting skeletal muscle. Inhalational agents (isoflurane, sevoflurane, desflurane) may be used with or without IV agents.

Intraoperatively, α blockade is continued with phentolamine, a competitive α1- and α2-receptor blocker that is the single best anti-hypertensive in managing the hypertensive crises of pheochromocytoma. The most common side effect of phentolamine is reflex tachycardia caused by the baroreceptor reflex following α2 blockade. Labetalol should be administered to control tachycardia. Calcium channel blockers and nitroprusside, although sporadically useful in controlling hemodynamic fluctuations, do not achieve the same successful results as does phentolamine. Based on the anesthesiologist’s preference, IV nitroprusside (1-2 mcg/kg) and sublingual nifedipine can be used as second-line therapies. However, the combination of phentolamine and labetalol ideally renders the use of other antihypertensives unnecessary.

Phentolamine should be titrated intravenously in 5-mg increments. One technique is to inject 5 mg of phentolamine after induction, and before the tumor is mobilized. With the surgeon and anesthesiologist in close communication, the surgeon is requested to stop if necessary so that additional phentolamine can be administered. Thus, control of blood pressure is maintained during tumor resection.

The over-administration of phentolamine may lead to transient hypotension. In cases of cardiovascular instability, the treatment of hypotension with a pressor—such as ephedrine or another β-adrenergic agent—can lead to significant ventricular irritability, including ventricular tachycardia or even...
fibrillation. Thus, careful dosing with phentolamine is extremely important; however, at times, proper dosing can be difficult given the unexpected extreme rises in blood pressure.

Transient hypotension induced by phentolamine is treated with fluid administration and watchful waiting for a natural rise and return of blood pressure to normal. In severe symptomatic cases, magnesium can be infused in addition to phentolamine and labetalol. Maintaining a plasma level below 2 mcg/mL (to avoid potentiating muscle relaxation) decreases catecholamine levels and hemodynamic fluctuations, and blunts the effects of intubation.6

Following ligation of the vein draining the pheochromocytoma, IV fluid administration is essential for volume expansion. The sudden drop in catecholamines can lead to significant hypotension. Combined colloid and crystalloid replacement is appropriate. Pressors may be necessary but are best avoided, and contraindicated if the patient is hypovolemic. Often the hypotension of pheochromocytoma is refractory to agents such as norepinephrine, epinephrine, and dopamine because of the desensitization of sympathetic receptors to previous persistently high levels of catecholamines.8

Glycemic changes should be monitored by the anesthesiologist. Hyperglycemia associated with increased catecholamine secretion may require insulin. It almost always resolves with removal of the tumor. Hypoglycemia may develop after tumor resection because of rebound hyperinsulinism without the inhibitory effect of norepinephrine on insulin secretion.

Medications That Trigger Catecholamine Release

Several medications have been shown to trigger the release of catecholamines from pheochromocytomas (Table 2).

The pressor effects of metoclopramide are well established. Although the mechanism is unclear, metoclopramide can cause a serious or even fatal hypertensive crisis. Metoclopramide should be avoided not only in patients with pheochromocytoma, but also in those patients with a particularly labile blood pressure that could be caused (albeit very rarely) by this tumor.

Pentazocine and droperidol also can increase the release and circulating levels of catecholamines. Droperidol additionally inhibits reuptake of catecholamines into nerve terminals. Any medication that induces the release of histamine should be avoided, including morphine and atracurium. Even small amounts of histamine can lead to a large release of catecholamines from pheochromocytomas, although practitioners have used morphine and atracurium in patients without adverse effects. Selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, imipramine, and curare all have been implicated in provoking the release of catecholamines.12,32

| Table 2. Medications Reported To Trigger Catecholamine Release In Pheochromocytomas |
|---------------------------------|---------------------------------|
| Atracurium                      | ß blockers                      |
| Curare                          | Droperidol                     |
| Imipramine                     | Metoclopramide                 |
| Monoamine oxidase inhibitors   | Opioids                        |
| Pentazocine                    | Selective serotonin reuptake inhibitors |
|                                | Many of these medications—particularly ß blockers and opioids—have been used in cases with pheochromocytomas without incident. Patients must be treated on an individual basis. |
Management of the Case Presented

In this case, induction of anesthesia was achieved with a combination of midazolam, fentanyl, propofol, and vecuronium. After uneventful endo-intubation of the patient, an arterial cannula was placed and prophylactic antibiotics were administered. Resection of the tumor was difficult because of its deep location. The surgery lasted more than 6 hours, but was otherwise uneventful. The patient’s vital signs were stable throughout; blood pressure ranged from 100-170/50-80 mm Hg, and pulse rate ranged from 75 to 110 beats per minute. The patient received a total of 925 mcg of fentanyl. Anesthesia was maintained with isoflurane, oxygen, and nitrous oxide. Urine output was 500 mL and estimated blood loss was 500 mL. Three liters of crystalloids and 500 mL of colloids were infused.

At the conclusion of surgery, the patient was awakened and extubated without difficulty. He was transported to the recovery room in stable condition. Vital signs including blood pressure were stable. Chemistry panel findings were within normal limits; hematocrit was 40%. At the time of the patient’s discharge from the recovery room 5 hours later, his vital signs included blood pressure, 120/50 mm Hg; pulse rate, 85 beats per minute; and respiratory rate, 14 breaths per minute. The patient indicated at that time that he was not experiencing pain.

Several hours after being transferred to the ward, the patient was found to be asystolic, pulseless, apneic, and with evidence of emesis. Immediate resuscitation was performed but the patient could not be revived.

A postmortem examination revealed an incidentaloma. It is possible that the patient had experienced episodes of postoperative pain (not controlled by patient-controlled analgesia) which caused the release of catecholamines. The catecholamines then could have caused either a hypertensive crisis or cardiac arrhythmias, in turn leading to the patient’s death. Thus, an undiagnosed pheochromocytoma should be included as a cause of death. A pheochromocytoma was not seen on radiographic images and the patient had not been screened for biochemical markers given that he was asymptomatic and his medical history included resection of bilateral pheochromocytomas.

Conclusion

Patients with pheochromocytoma may present in a variety of ways, beyond the well-known cases described in textbooks. Clinicians must be prepared to identify and treat such atypical patients, particularly in the aging population with an increased incidence of these tumors. When anesthesiologists find patients with high lability in blood pressure perioperatively, pheochromocytoma should be ruled out. Our case raises the question of whether every patient with vHLS or with MEN type 2A or 2B should be fully evaluated for pheochromocytoma, regardless of symptomatology or history of pheochromocytoma. Such evaluation is not a universally accepted standard of care, but should be considered. Our case also emphasizes the need for careful postoperative monitoring—possibly in an intensive care setting—for 24 to 48 hours.

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REFERENCES


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Post-test

1. Which of the following is a characteristic of the patient with pheochromocytoma?
   a. Tachycardia
   b. Hypertension
   c. Sweating
   d. All of the above

2. Which therapy is preferable in the patient with coexisting von Hippel-Lindau syndrome (vHLS) and pheochromocytoma?
   a. The pheochromocytoma is removed first.
   b. The renal cell carcinoma associated with vHLS is removed first.
   c. After pretreatment with antihypertensives, either surgery may take precedence.
   d. The surgery is delayed until all laboratory test results are confirmed.

3. The preoperative preparation of a patient with pheochromocytoma includes:
   a. administering 50 mg per day of phenoxybenzamine 2 days before surgery
   b. therapy with a competitive and reversible β-adrenergic blocker
   c. administering 40 mg per day of phenoxybenzamine with an increase to 80 to 120 mg per day over 2 weeks
   d. administering a calcium channel blocker as first-line therapy

4. The medication that is least likely to trigger a release of catecholamines is:
   a. metoclopramide
   b. droperidol
   c. any opioid
   d. ketorolac
5. Which of the following anesthetic regimens is least likely to cause a hypertensive crisis in a patient with pheochromocytoma?
   a. Thiopental, atracurium, remifentanil
   b. Propofol, sevoflurane, vecuronium, fentanyl
   c. Propofol, succinylcholine, morphine
   d. Etomidate, midazolam, pancuronium

6. Postoperatively, the preferred management of the patient with vHLS after laparoscopic removal of a renal cell carcinoma is:
   a. early discharge to home to prevent a hospital-acquired infection
   b. an overnight infusion of sodium nitroprusside
   c. adequate pain control and cardiorespiratory monitoring for 24 to 48 hours
   d. fluid loading to prevent hypotension resulting from removal of a catecholamine-secreting tumor

7. Which is the drug of choice to control blood pressure intraoperatively in the patient with pheochromocytoma?
   a. Nitroglycerin
   b. Labetalol
   c. Phentolamine
   d. Sevoflurane

8. Cardiovascular changes after the resection of a pheochromocytoma include:
   a. hypotension refractory to epinephrine and norepinephrine
   b. hyperglycemia
   c. hypertension and tachycardia due to volume depletion
   d. all of the above

9. Which type of cardiomyopathy is most commonly associated with pheochromocytoma?
   a. Dilated
   b. Hypertrophic
   c. None; it has not been described
   d. All types; cardiomyopathy is a common occurrence

10. In the patient with vHLS, findings are most likely to include:
    a. capillary hemangioblastomas of the retina
    b. erythrocytosis
    c. pancreatic cysts
    d. all of the above