VARIANTS OF PHEOCHROMOCYTOMA AND THEIR ANESTHETIC IMPLICATIONS

– A Case Report And Literature Review –

KATHRYN DORTZBACH, DANIEL M GAINSBURG* AND ELIZABETH AM FROST**

Anesthesiologists are trained to appreciate and respond appropriately to the considerable consequences of pheochromocytomas. It is however, less well appreciated that these tumors may be associated with other syndromes that can also carry significant anesthetic risk. We describe the case of a young man who had a rare disease in combination with multiple pheochromocytomas and suffered a fatal outcome after anesthesia. Possible causes for this disaster are suggested.

Case History

A 23 year-old male with a past medical history significant for Von Hippel-Lindau (VHL) syndrome presented for a laparoscopic right partial nephrectomy. The patient was diagnosed with renal cell carcinoma (RCC), which was found incidentally on CT scan, originally performed to assess for rib fractures after a motor vehicle accident. His past surgical history was significant for craniotomy with tumor resection secondary to hemangiomas related to VHL, and a right total adrenalectomy and left partial adrenalectomy both to remove pheochromocytomas. These surgeries were performed nine and eight years prior, respectively. The patient showed no other recurrences of lesions secondary to VHL other than the RCC. On preoperative assessment, the patient weighed 100 kg and stood 183cm tall. His blood pressure was 125/78 and his pulse was 80. Medications included only a muscle relaxant, which he took for back spasms following the accident He was otherwise asymptomatic. He reported a possible allergy to penicillin as a child.

In the operating room, induction was performed and an arterial cannula was placed following intubation. Gentamycin 80mg and clindamycin 600mg were given as antibiotic prophylaxis. Tumor resection was difficult due to its deep location. The case lasted over six hours and was otherwise uneventful. Vital signs were stable throughout with a blood pressure ranging from 100-170/50-80 and a pulse rate from 75-110. He received a total of fentanyl 925mcg, and was maintained with isoflurane, oxygen and nitrous oxide. Urine output was 500 ml and the estimated blood loss was 500 ml. Crystalloids, 4 liters were infused. At the end of the case, the patient was awakened and extubated without difficulty. He was transported to the recovery room in stable condition. Vital signs were blood pressure of 140/70, pulse rate 90, respiratory rate 20, temperature 37.4. Chemistry panel was within normal limits and the hematocrit was 40.

Vital signs upon discharge from the recovery room five hours later were blood pressure of 120/50, pulse rate 85, respiratory rate 14. The patient indicated at that time that he was not experiencing pain.

Around 4:45 am, several hours after he was transferred to the ward, the patient was found asystolic, pulseless and apneic and with evidence of emesis. Immediate resuscitation was performed but the patient could not be revived.

Attending Anesthesiologist, New York Eye & Ear Infirmary, New York, NY.
* MD, Assistant Professor.
** MD, Professor.
Dept of Anesthesiology, Mount Sinai Medical Center, New York NY.

Introduction

Pheochromocytoma is one of the more challenging medical conditions faced by the anesthesiologist. Its hallmark paroxysmal hypertensive crises and cardiac manifestations including sinus tachycardia and bradycardia as well as arrhythmias, require the anesthesiologist to exercise the highest degree of vigilance. Significant improvements have been made in the management of pheochromocytomas since the first reports of their resection in the mid to late 1920s. Today, the mortality rate is less than 5%[1]. With greater awareness in diagnosing and treating pheochromocytomas, anesthesiologists can work perioperatively to reduce the mortality rate even further.

Among patients diagnosed with hypertension, roughly 0.1 percent are attributable to pheochromocytomas[2], a small but not insignificant statistic given the incidence of hypertension. Also, these patients have a medical condition, which in most instances can be cured if diagnosed and treated correctly. Patients who remain undiagnosed are at great risk for further morbidity and high mortality, particularly if they must undergo surgical procedures. Of those patients with undiagnosed pheochromocytomas, as many as 25-50% die from complications occurring during induction of anesthesia or during anesthesia for procedures for other medical conditions[3].

Pheochromocytomas are very vascular tumors comprised of chromaffin tissue, which secretes varying quantities of epinephrine and norepinephrine which account for the clinical presentation. 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 at the bifurcation of the aorta[3].

While isolated pheochromocytomas of a non-familial etiology comprise most cases, it is important to understand the threat of a pheochromocytoma in more complex clinical settings. Approximately 5% of pheochromocytomas are associated with other syndromes such as VHL[3]. Our case serves as an example of one of many atypical contexts in which pheochromocytomas arise. Pheochromocytomas in the setting of VHL, and other familial syndromes, as well as in the setting of recurrence and clinically silent cases and the general management are presented.

Incidence and Epidemiology

The greatest incidence of pheochromocytomas occurs in the fourth and fifth decades.

In the adult population, roughly 80% of tumors are solitary and unilateral, occurring in one of the adrenal glands. The remaining 20% are divided between bilateral lesions or extraadrenal masses. "The rule of 10s" refers to the statistic that 10% of tumors are extraadrenal, 10% are bilateral and 10% are malignant. Malignant spread is most typically to the liver via lymphatics and venous routes[3]. Recurrence is estimated at 8%[1]. Five percent of pheochromocytomas are inherited, either as an isolated phenomenon or as part of a familial syndrome.

Symptoms

Catecholamine release from pheochromocytomas accounts for most symptoms, usually headaches, palpitations and sweating. Both epinephrine and norepinephrine are synthesized, stored and secreted in pheochromocytomas. However, every tumor releases a different ratio of the two catecholamines and some tumors contain only one catecholamine. Epinephrine secreting tumors produce palpitations, sweating, heat intolerance, tremulousness, pallor and flushing, headache and weight loss. With the potential for very strong beta-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[3].

Tumors that secrete both catecholamines exert a wide spectrum of symptoms. Few patients are asymptomatic. Around 50% of patients experience nonparoxysmal hypertension, either sustained or labile. The rest experience paroxysmal elevated blood pressure with the worst symptoms associated with the greatest fluctuations in plasma catecholamine levels. The frequency of symptoms is also variable, as patients may live for years without a recurrent attack while others suffer over 20 attacks of sudden onset daily. Most attacks last for a few minutes to a few hours but some may be as short as several seconds and others may persist for days[1-3].

In addition to hypertension, pheochromocytomas

can cause deleterious but less common cardiac manifestations. Sinus tachycardia, sinus bradycardia, supraventricular dysrhythmias and premature ventricular contractions have all been reported. Patients without a history of coronary artery disease may suffer anginal pain and myocardial infarctions, believed to be a result of catecholamine induced coronary artery spasm. Electrocardiographic changes include right and left bundle branch blocks, non-specific ST segment and T wave changes and prominent U waves[3].

Catecholamine cardiomyopathies are rare and are presumed to be associated with a longer duration of disease and exposure to catecholamines. In the most severe cases, these cardiomyopathies can lead to heart failure and death. The mechanism has not been fully delineated but persistent hypertension can cause a hypertrophic cardiomyopathy. Dilated cardiomyopathies are less common[4].

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 be due to desensitized alpha-adrenergic receptors or sympathetic reflexes from the high amount of circulating catecholamines or volume depletion related to hypertension[4]. Patients with pheochromocytomas in the bladder wall may present with hematuria and bladder spasms with polyuria.

Diagnosis and Laboratory findings

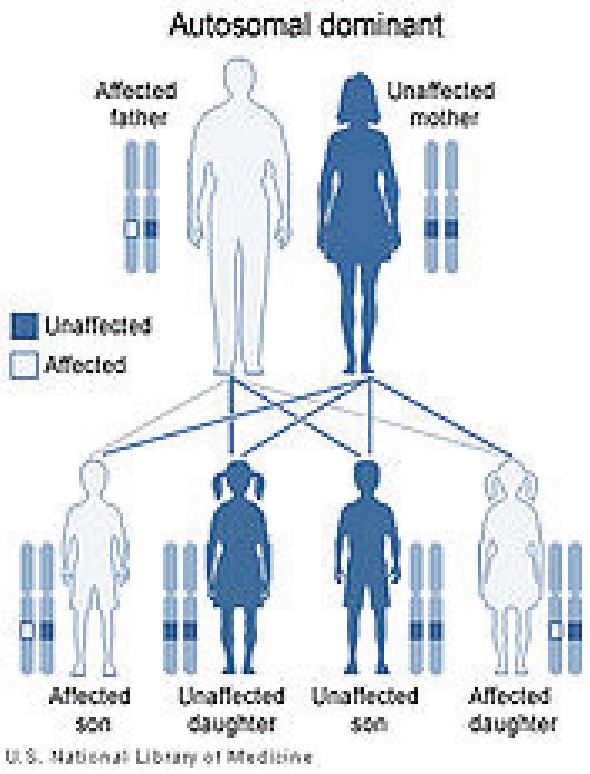
The first step in diagnosis is often made by measuring 24 hour urinary metanephrine and vanillylmandelic acid levels and plasma catecholamines. No test is perfect with each having different degrees of sensitivity and specificity. The sensitivity of plasma free metanephrines is approximately 96-100%. Specificity is lower, between 82-96%. In comparison, urine metanephrines and catecholamines have a greater specificity of 98% and a lower sensitivity of 90%[5]. Any of the biochemical markers could be negative despite positive clinical findings and the presence of a tumor. Conversely, there are several drugs that can lead to false positive results for catecholamines and metanephrines, falsely suggesting a diagnosis of pheochromocytoma. The list includes antipsychotics, L-dopa, tricyclic antidepressants, clonidine, phenoxybenzamine, caffeic acid (found in decaffeinated coffee), ethanol, paracetamol and substantial physical stress[5]. The clonidine suppression test can be used to rule out a rise in catecholamines due to other causes[6]. Because a pheochromocytoma secretes catecholamines that are free from neurogenic control, administration of clonidine will not result in suppression. To confirm a diagnosis, imaging studies include CT scan, magnetic resonance imaging (MRI) and meta-iodobenzylguanidine scintiscan (MIBG). CT and MRI are comparable in sensitivity, 98% and 100% respectively but both have lower specificities, CT with 70% and MRI with 67%. MIBG 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 as an isolated finding or in association with a syndrome including VHL, Multiple Endocrine Neoplasia (MEN) type 2a and type 2b, and von Recklinghausen neurofibromatosis. For the anesthesiologist, pheochromocytoma is generally the most threatening component of both VHL and MENIIA/IIB[8,9]. Patients with any of these syndromes should be evaluated preoperatively for pheochromocytoma regardless of their medical history and whether or not they show any signs or symptoms of catecholamine secreting tumors.

Von Hippel-Lindau Syndrome is an autosomal dominant disease that has variable expression and incomplete penetrance (Fig. 1). The disease was first described over 100 years ago. Eugen von Hippel described angiomas in the eye in 1904[10]. Arvid Lindau described angiomas of the cerebellum and spine in 1927[11].

Fig. 1
Von Hippel-Lindau Syndrome is an autosomal dominant disease



Findings include capillary hemangioblastomas of the retina (seen in 60-70% of patients), and hemangioblastomas of the central nervous system (CNS) (30-70% of patients). Most of the CNS lesions are located in the cerebellum. Less commonly, erythrocytosis, pancreatic and renal cysts, renal cell carcinoma and hypernephroma are seen. Pheochromocytoma occurs in about 10%[12]. and is more likely to be bilateral and to recur[13]. VHL patients tend to be younger at the age of diagnosis and have their pheochromocytomas diagnosed early, likely because of the higher level of suspicion for pheochromocytoma and its known association with VHL. VHL results from a mutation in the tumor-supressor gene on chromosome 3p25.3[14-19]. 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 a person's lifetime, the cell has no working copies of the gene and produces no functional VHL protein. A lack of this protein allows tumors characteristic of von Hippel-Lindau syndrome to develop. Since both alleles need to be mutated for the disorder to develop, it would be likely to conclude that the mutation is recessive. However, studying the patterns of heredity,VHL is, paradoxically, an autosomal dominant disorder because people 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 percent of cases. In about 20 percent 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 of a mutation occuring in a cell where both alleles are previously normal is quite small. Also, the first mutation must be followed by a second for the syndrome to develop.

VHL may be diagnosed when one of its associated diseases causes discomfort[20-26]. Angiomatosis, hemangioblastomas, pheochromocytoma, renal cell carcinoma, pancreatic cysts and café au lait spots are all associated with VHL. Angiomatosis occurs in 37.2% of patients presenting with VHL and usually occurs in the retina, however other organs can be affected. As a result, loss of vision is very common. On average only about 20% of people with VHL get pheochromocytomas. The risk of developing such tumors (which are usually histologically benign) appears to hinge on the precise nature of the mutation responsible for VHL disease in a specific family. In kindreds with VHL who demonstrate a deletion or protein-truncating mutation of the VHL gene (type 1 VHL), the risk for pheochromocytoma is less than 10%. However, the risk is approximately 50% for pheochromocytoma development in kindreds with a missense mutation (type 2 VHL).

There is a wide variation in the age of onset of the disease, the organ system affected and the severity of effect suggesting that the second mutation can occur in different types of cells and at various times of a person's life.

If a patient with VHL has coexisting lesions or disorders that require surgical correction in addition to the removal of the pheochromocytoma, resection of the pheochromocytoma is prioritized. In patients with CNS lesions, potential complications exist. If the intracranial mass is addressed first, the anesthesiologist

is faced with the potential for extreme hypertension leading to intracranial bleeding intraoperatively and postoperatively. If the decision is made to resect the pheochromocytoma first, required use of vasodilators to control hypertension may increase cerebral blood flow (CBF) 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 takes precedence[27].

Multiple endocrine neoplasias (MEN) comprise three different familial syndromes inherited as autosomal dominant traits[8]. MEN I does not have pheochromocytoma as part of its profile and therefore does not pertain to this case. MEN IIA (Sipple's syndrome) includes medullary thyroid cancer (97%), pheochromocytoma (50%) and hyperparathyroidism (20%) and is thus more similar to VHL regarding the presentation of pheochromocytoma. MEN IIB, rarer than IIA, is associated with medullary thyroid cancer, pheochromocytoma and a Marfanoid body habitus and mucosal neuronal syndrome with mucosal neuromas and intestinal ganglioneuromas. Also, in MEN IIB, the tumor generally presents late and is rarely malignant or bilateral[9].

In the case of MEN IIA patients, if the pheochromocytoma is resected before removal of the parathyroid glands, the calcium level must be checked as most patients have asymptomatic hypercalcemia. Symptomatic patients may complain of fatigue, weakness in general or proximal muscle weakness, confusion, polyuria, and polydypsia. Patients may also have findings of hyporeflexia, pseudogout, anemia, subperiosteal bone resorption, and renal stones. Abnormal EKG findings include a shortened QT interval and prolonged PR interval[8]. Cardiac dysrhythmias are the most important potential complication of hypercalcemia. QT intervals do not necessarily correlate with changes in calcium concentrations, thus blood gas analyses must be done in conjunction with blood calcium levels. Management of hypercalcemia includes intravenous fluid administration with sodium-containing solutions, which dilute the calcium and inhibit renal reabsorption. Urine output must be closely monitored to assess renal dysfunction.

Other concerns for the anesthesiologist in these cases include muscle relaxant dosing, positioning of the patient and the potential for airway compromise. Muscle relaxant effects may be enhanced by hypercalcemia. Preoperative assessment of muscle weakness must be documented to record baseline and to tailor muscle relaxant administration to the patient's requirements. Careful positioning of the patient with appropriate padding is important to avoid pathological fractures from osteoporosis[8]. Although bilateral tumors frequently occur with medullary thyroid cancer, they are rarely large enough to compress the airway. However, airway compromise must be considered and a difficult airway cart made available.

For any patient with VHL or MENIIA/B presenting for surgery, the diagnosis of 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 recurrences and/or for pheochromocytoma on the unresected side.

Asymptomatic Pheochromocytoma

A subset of pheochromocytomas known as adrenal incidentalomas is clinically silent. These tumors likely make a substantial contribution to the statistic that fifty percent of pheochromocytomas are discovered post-mortem[6]. With advancements in imaging, these lesions are estimated at a prevalence of almost 3% in middle age to nearly 10% in the elderly[13]. These pheochromocytomas may be hormonally active or inactive and therefore may not be detected during screening[12]. While incidentalomas may secrete catecholamines at a level that leaves the patient asymptomatic, the lesions are not benign. There has been an increasing trend to treat these subclinical tumors given the uncertainty of their association with increased morbidity.

The undiagnosed pheochromocytoma suspected intraoperatively during surgery for another medical condition can have devastating consequences. The mortality rate is as high as 80%, during anesthesia. Any hypertensive patient not taking antihypertensive medications presenting for surgery who complains of orthostatic hypotension, should be tested for a diagnosis of pheochromocytoma. As many as 10% of cases of orthostatic hypotension may be due to

pheochromocytomas[6,28]. Also any patient for surgery to remove an adrenal mass must be evaluated for pheochromocytoma.

Preoperative Management

Part of the key to avoiding intraoperative complications in the removal of pheochromocytomas is to ensure preoperative optimization. The most important goal is to achieve blood pressure control prior to surgery. The alpha adrenergic blocker, phenoxybenzamine is first line therapy. Phenoxybenzamine is a non-selective alpha blocker targeting both alpha 1 and alpha 2 receptors. The blockade is noncompetitive and irreversible. Phenoxybenzamine can be started at least two weeks prior to the scheduled surgery on an outpatient basis to allow for maximal alpha blockade and restoration of blood volume given that chronic alpha constriction causes volume depletion. The protocol for preoperative alpha blockade requires initially phenoxybenzamine 40 mg per day followed by a gradual increase to 80 to 120 mg per day. Postural hypotension is the most common side effect. While this relatively simple intervention cannot promise the prevention of fluctuations in blood pressure intraoperatively, it has been estimated to decrease perioperative mortality from 45% to 3%[6].

Even patients without cardiovascular symptoms despite the diagnosis of pheochromocytoma may benefit from alpha blockade treatment. Apparent preoperative hemodynamic stability does not preclude severe intraoperative hemodynamic fluctuations including increased systemic vascular resistance following induction of anesthesia and hypotension following tumor resection. Calcium channel blockers have shown benefit in patients who are generally normotensive but with paroxysmal hypertension[8]. The advantage is that they do not cause orthostatic hypotension; however alpha blockers are still considered preferable in preoperative management. Beta blockade is the second component to preoperative preparation if the patient has tachycardia, arrhythmias, or a history of coronary artery disease. Alpha-adrenergic block must be established prior to beta-blockade. If beta-blocking agents are given first, unopposed alpha-blockade and its consequential vasoconstriction could lead to a life threatening hypertensive crisis. To ensure optimization for surgery, it is highly recommended that the patient meet the Roizen criteria for sufficient alpha blockade (Table 1)[29].

Table 1
Roizen's Criteria for Appropriate Preoperative Alpha Blockade and Surgical Optimization

• No in hospital pre-surgical blood pressures measuring higher than 165/90 24 hours prior to surgery.
• No orthostatic hypotension with blood pressure measuring lower than 80/45.
• No EKG showing ST-T changes one week prior to surgery.
• No more than one premature ventricular contraction every five minutes.

An echocardiogram should be performed preoperatively to assess catecholamine related cardiomyopathy. In patients with cardiomyopathy, a longer period of preoperative preparation, while not always practical (some have suggested that as long as six months treatment with alpha-blockade is necessary) may help reverse myocardial dysfunction[30]. Untreated, a heart stressed by high levels of circulating catecholamines and arterial hypertension may not compensate for postoperative hypotension due to catecholamine withdrawal.

Intraoperative Management

Surgical resection cures 90% of patients. Laparoscopic removal of pheochromocytomas has become increasingly common, provided there is no local invasion and the mass is less than 6cm. Large, recurrent or invasive pheochromocytomas should be removed by laparotomy[31]. While the laparoscopic approach results in a shorter recovery time, both laparoscopic and open approaches are equal in terms of overall survival[7]. Neither approach has been proven superior regarding anesthetic management.

The greatest intraoperative concern is the 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 the surgery but 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 entering the operating room and placing standard ASA monitors, obtaining intravenous access, preferably at two reliable sites is desirable. Arterial cannulation is necessary and should be in place prior to induction. The use of central venous monitoring and pulmonary artery catheterization depends upon the clinical condition and should be used in cases of cardiomyopathy and documented preoperative cardiac compromise.

Induction agents should be titrated slowly to maintain normotension. A short acting narcotic such as fentanyl, with its minimal myocardial depression, in combination with a sedative/hypnotic is preferable to a sedative/hypnotic agent alone. It is important to achieve an adequate depth of anesthesia such that the patient does not respond to the stimulus of intubation[8,31]. Vecuronium or rocuronium may be used for muscle relaxation as these agents have few if any cardiovascular effects. Pancuronium should be avoided because of its sympathomimetic effects. Histamine release caused by atracurium can increase the release of catecholamines. Succinylcholine should theoretically be avoided because of its possible potentiation of catecholamine release from contracting skeletal muscle[6,8]. Inhalational agents (isoflurane, sevoflurane, desflurane) may be used with or without intravenous agents.

Intraoperatively, alpha blockade is continued with phentolamine. Phentolamine is a competitive alpha 1 and alpha 2 receptor blocker[32] and is the single best antihypertensive treatment in managing hypertensive crises due to pheochromocytoma. Its most common side effect is reflex tachycardia due to the baroreceptor reflex following alpha 2 blockade. Labetalol should be used to control tachycardia. Calcium channel blockers and nitroprusside, while sporadically helpful in controlling hemodynamic fluctuations, do not have the same success as phentolamine. Based upon the anesthesiologist's preference, intravenous nitroprusside (1-2 mcg/kg) and sublingual nifedipine can be used as second line therapies. However, the combination of phentolamine and labetalol ideally render unnecessary the use of other antihypertensives[8].

Phentolamine should be titrated in 5 mg increments intravenously. One technique is to inject phentolamine 5mg after induction, and before the tumor is mobilized. With close communication between the surgeon and anesthesiologist, the surgeon is asked to stop if necessary so that more phentolamine can be administered. Thus, blood pressure control is maintained during tumor resection[8]. Over administration of phentolamine may lead to transient hypotension. Cardiovascular instability may be such that treatment of hypotension with a pressor such as ephedrine or other beta adrenergic agents may rarely lead to significant ventricular irritability including ventricular tachycardia or even fibrillation. Thus, careful dosing of phentolamine is extremely important, however at times very difficult given the unexpected extreme rises in blood pressure. Transient hypotension induced by phentolamine may be treated best with fluid administration and watchful waiting for a natural rise and return of blood pressure to normal. In severe symptomatic cases, a magnesium infusion can be used in addition to phentolamine and labetalol. Maintaining plasma levels < 2ug/ml (not to potentiate muscle relaxation) decreases catecholamine levels and hemodynamic fluctuations and blunts the effects of stimulation during intubation[6].

Following ligation of the vein draining the pheochromocytoma, intravenous fluid administration is essential for volume expansion. The sudden drop in catecholamines can lead to significant hypotension, requiring aggressive fluid replacement with a combination of crystalloids and colloids. Pressors may be necessary to maintain blood pressure in severe hypotension but they 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 the previously persistently high levels of catecholamines[8].

Throughout the case, aggressive intravenous fluid resuscitation is important to account for chronic volume depletion, hypotension following catecholamine withdrawal, and intraoperative blood loss, which is usually minimal with a laparoscopic approach.

The anesthesiologist should also monitor for

glycemic changes. Hyperglycemia associated with increased catecholamine secretion may require insulin. It almost always resolves with removal of the tumor. Hypoglycemia may follow 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 by which it does this is unclear, metoclopramide can cause a serious or even fatal hypertensive crisis. It should be avoided not only in patients with pheochromocytomas but also in all patients with particularly labile blood pressure that could very rarely be due to this tumor.

Table 2
Medications Reported to Trigger the Release of Catecholamines in Pheochromocytomas

- Metoclopramide.
- Pentazocaine.
- Droperidol.
- Atracurium.
- SSRIs.
- MAO inhibitors.
- Imipramine.
- Beta-blockers.
- Opioids.
- Curare.

Many of the above medications particularly beta-blockers and opioids have been used in cases with pheochromocytomas without incidence. Patients must be treated on an individual basis.

Pentazocaine and droperidol can also increase release and circulating levels of catecholamines. Droperidol additionally inhibits the reuptake of catecholamines into nerve terminals. Any medications that induce histamine release should be avoided, including morphine and atracurium. Even small amounts of histamine can lead to large release of catecholamines from pheochromocytomas, although practitioners have used morphine and atracurium without repercussions. Selective serotonin reuptake inhibitors (SSRI), monoamine oxidase (MAO) inhibitors, imipramine, and curare have all been implicated in provoking the release of catecholamines[12,33].

Conclusion

In the case of our 23 year-old male, post mortem examination revealed an incidentaloma. It is possible that the patient had episodes of postoperative pain, not controlled by patient controlled analgesia, which caused the release of catecholamines. These catecholamines could have then caused either a hypertensive crises or cardiac arrhythmias in turn leading to the patient's demise. Thus, an undiagnosed pheochromocytoma should be included as one of the causes of the patient's death. It was not seen on radiographic images and the patient had not been screened for biochemical markers given he was asymptomatic and had had a history of prior resection of bilateral pheochromocytomas. This case raises the question of fully evaluating for pheochromocytomas in every patient with VHL or with MENIIA/B regardless of symptomatology or previous history of pheochromocytoma. Such evaluation is not a universally accepted standard of care but should be considered.

Pheochromocytomas have variable ways in which they may present beyond the well known text book case. Clinicians must be prepared to identify and treat patients with such atypical presentations, particularly with the aging population and their increased incidence of these tumors. In instances where anesthesiologists find great lability in perioperative blood pressures, there should be a higher level of suspicion for pheochromocytoma. Our case especially emphasizes the need for careful post-operative monitoring, possibly in an intensive care unit setting for 24-48 hours.

References

1. Williams DT, Dann S and Wheeler MH: Pheochromocytoma-views on current management. *European Journal of Surgical Oncology*; 2003, 29:483-490.
2. Landsberg and Young JB: Pheochromocytoma. Harrison's Principles in Internal Medicine. 14th edition. 1998. TR Harrison. McGraw-Hill. New York, 2057-2060.
3. Roizen MF: Anesthetic Implications of Concurrent Diseases. Anesthesia. 5th edition. 2000. RD Miller. Churchill Livingstone. New York, 924-925.
4. Munakata M, Aihara A, Imari Y, Noshiro T, Ito S, and Yoshinaga K: Altered sympathetic and vagal modulations of the cardiovascular system in patients with pheochromocytoma. *American Journal of Hypertension*; 1999, 12:572-580.
5. Tahrani AA and Macleod AF: A diagnostic dilemma in diagnosing and managing an incidental phaeochromocytoma. *Exp Clin Endocrinol Diabetes*; 2006, 114:204-207.
6. Myklejord DJ: Undiagnosed pheochromocytoma: the anesthesiologist nightmare. *Clinical Medicine & Research*; 2004, 2:59-62.
7. Bravo EL: Pheochromocytoma: current perspectives in the pathogenesis, diagnosis, and management. *Arq Bras Endocrinol Metabol*; 2004, 48:746-50.
8. Grant F: Anesthetic considerations in the multiple endocrine neoplasia syndromes. *Current Opinion in Anaesthesiology*; 2005, 18:345-352.
9. Ailun L, Xiangyang G, Hongzhi R, Yuguang H, and Tiehu Y: Clinical features and anesthetic management of multiple endocrine neoplasia associated with pheochromocytoma. *Chinese Medical Journal*; 2003, 116:208-211.
10. von Hippel E: Ueber eine sehr seltene Erkrankung der Netzhaut. *Albrecht von Graefes Arch Ophthal*; 1904, 59:83-106.
11. Lindau A: Zur Frage der Angiomatosis Retinae und Ihrer Hirncomplikation. *Acta Ophthal*; 1927, 4:193-226.
12. Gurunathan U and Korula G: Unsuspected pheochromocytoma: von Hippel-Lindau disease. *Journal of Neurosurgical Anesthesiology*; 2004, 16:26-28.
13. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohour F, Chatellier G and Plouin PF: Year of diagnosis features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *The Journal of Clinical Endocrinology & Metabolism*; 2005, 90:2110-2116.
14. Wong WT, Agrón E, Coleman HR, et al: "Genotype-phenotype correlation in von Hippel-Lindau disease with retinal angiomatosis". *Archives of ophthalmology*; 2007, 125 (2):239-45.
15. Abbott MA, Nathanson KL, Nightingale S, Maher ER and Greenstein RM: The von Hippel-Lindau (VHL) germline mutation V84L manifests as early-onset bilateral pheochromocytoma. *Am J Med Genet A*; 2006, 140:685-90.
16. Beroud C, Joly D, Gallou C, Staroz F, Orfanelli MT and Junien C: Software and database for the analysis of mutations in the VHL gene. *Nucleic Acids Res*; 1998, 26:256-8.
17. Bryant J, Farmer J, Kessler LJ, Townsend RR, and Nathanson KL: Pheochromocytoma: the expanding genetic differential diagnosis. *J Natl Cancer Inst*; 2003, 95:1196-204.
18. Glasker S: Central nervous system manifestations in VHL: genetics, pathology and clinical phenotypic features. *Fam Cancer*; 2005, 4:37-42.
19. Maher ER and Eng C: The pressure rises: update on the genetics of phaeochromocytoma. *Hum Mol Genet*; 2002, 11:2347-54.
20. Molino D, Sepe J, Anastasio P and De Santo NG: The history of von Hippel-Lindau disease. *J Nephrol*; 2006, 19 Suppl, 10:S119-23.
21. Kreusel KM: Ophthalmological manifestations in VHL and NF 1: pathological and diagnostic implications. *Fam Cancer*; 2005, 4:43-7.
22. Kreusel KM, Bechrakis NE, Krause L, Neumann HP and Foerster MH: Retinal angiomatosis in von Hippel-Lindau disease: a longitudinal ophthalmologic study. *Ophthalmology;* 2006, 113:1418-24.
23. Maher ER, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, Sampson J, Williams A, Ferguson-Smith MA and Morton N: Von Hippel-Lindau disease: a genetic study. *J Med Genet*; 1991, 28:443-7.
24. Molino D, Sepe J, Anastasio P and De Santo NG: The history of von Hippel-Lindau disease. *J Nephrol*; 2006, 19 Suppl, 10:S119-23.
25. Wanebo JE, Lonser RR, Glenn GM and Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. *J Neurosurg*; 2003, 98:82-94.
26. Webster AR, Maher ER and Moore AT: Clinical characteristics of ocular angiomatosis in von Hippel-Lindau disease and correlation with germline mutation. *Arch Ophthalmol*; 1999, 117:371-8.
27. Umgawar M, Rajender Y, Purohit A, Sastry RA, Sundaram C and Rammurti S: Anesthetic management of von Hippel-Lindau syndrome for excision of cerebellar hemangioblastoma and pheochromocytoma surgery. *Anesthesia & Analgesia*; 1998, 86:673-674.
28. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y and Bornstein SR: The clinically unapparent adrenal mass: update in diagnosis and management. *Endocrine Reviews*; 2004, 25:309-340.
29. Roizen MF, Schreider BD and Hassan SZ: Anesthesia for patients with pheochromocytoma. *Anesthesiol Clin North Am*; 1987, 5:269-75.
30. Shupak RC: Difficult anesthetic management during pheochromocytoma surgery. *Journal of Clinical Anesthesia;* 1999, 11:247-250.
31. Pederson LC and Lee JE: Pheochromocytoma. *Current Treatment Options in Oncology*; 2003, 4:329-37.
32. Mycek MJ, Harvey RA and Chaupe PC: Lippincott's Illustrated Reviews Pharmacology, 2nd edition. *Lippincott-Raven. Philadelphia*; 1992, pp. 71-71.
33. Anon: Phaeochromocytoma unmasked by drug therapy. *Prescrire int*; 2003, 12:181-2.