

Case Report

Undiagnosed Pheochromocytoma: The Anesthesiologist Nightmare

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ABSTRACT

A male, 62 years of age, presented to the operating room for the removal of a right adrenal mass. Induction of anesthesia triggered a severe hypertensive crisis resistant to high doses of nitroprusside, nitroglycerin and labetalol. The crisis was ultimately resolved with the administration of 5 mg bolus of phentolamine. Surgery was canceled, the patient was transported to the intensive care unit with a continuous drip of phentolamine.

High urinary and plasma catecholamines suggested the presence of pheochromocytoma. Three weeks of oral phenoxybenzamine therapy subsequently allowed uneventful induction of anesthesia and open adrenalectomy. Pathologic examination of the resected adrenal tissue confirmed the presence of pheochromocytoma.

Anesthetic drugs can exacerbate the life-threatening cardiovascular effects of catecholamines secreted by pheochromocytomas. Treating patients preoperatively with α -adrenergic blockade is helpful for reducing intraoperative hypertensive episodes. Postoperative administration of inotropic agents to correct hypotension due to catecholamine withdrawal may be required. Management of patients with pheochromocytoma remains a challenge for the anesthesiologist, despite the advent of new drugs and techniques.

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INTRODUCTION

Anesthetic management of any surgical patient with pheochromocytoma is challenging, particularly when the tumor has not been diagnosed. The incidence of pheochromocytoma is very low (2 people/million/year) with most tumors occurring between ages 20 and 50 years. Fifty percent of the cases are diagnosed only at post-mortem examination. A proportion of patients are diagnosed at the time of incidental surgery when induction of anesthesia may precipitate a hypertensive crisis. In this situation mortality is close to 80%.¹

Anesthetic drugs can exacerbate the life-threatening cardiovascular effects of catecholamines secreted by these tumors. Most pheochromocytomas secrete both epinephrine and norepinephrine. Pheochromocytomas are the secondary cause of hypertension in 0.1% of hypertensive patients. The symptoms that may accompany hypertensive crises are headache, palpitations, sweating, tremor, pallor or flushing. Complications from alarmingly high blood pressures include cerebrovascular hemorrhage, heart failure or arrhythmias, and myocardial infarction.

In this case, the patient presented with an undiagnosed pheochromocytoma, which led to a life-threatening hypertensive crisis at the time of induction of anesthesia that was unresponsive to strong antihypertensive drugs. This case serves to emphasize the importance of being vigilant and prepared for such unexpected occurrences.

CASE REPORT

A male, 62 years of age, undergoing a routine medical exam was found to have elevated levels of creatinine (2.5 mg/dL). Magnetic resonance imaging revealed a right adrenal mass (figure 1), an adrenalectomy was scheduled. The patient had a history of labile hypertension with episodes of angina relieved with nitroglycerin. Previous cardiac catheterization determined two-vessel coronary artery disease. A stress test showed no signs of acute ischemia. Other medical problems included elevated cholesterol, depression and familial tremor.

Preoperative status

MEDICATIONS

Medications included isosorbide mononitrate (120 mg daily), amlodipine besylate (5 mg daily), enalapril (20 mg daily), atorvastatin (40 mg daily), gemfibrozil (600 mg daily), aspirin (325 mg daily), potassium (20 mEq daily), nitroglycerin (as needed), and fluoxetine (20 mg daily).

PHYSICAL EXAM

On physical examination, the height of the patient was 67 inches, weight 84 kg. The American Society of Anesthesiologists (ASA) physical status classification was P3 (severe systemic disease). The airway Mallampati classification was 2 (mildly difficult). The patient had good mouth opening with a thyromental distance of more than 3 cm. The neck motion was appropriate. The patient seemed

anxious, there was a constant tremor, which was most prominent in the hands. The heart rate and rhythm were regular. There was a III/VI systolic murmur that was heard best at the upper right sternal border and no carotid bruits. Lungs were clear to auscultation bilaterally. The rest of the exam was unremarkable.

ELECTROCARDIOGRAM

Normal sinus rhythm with the presence of premature ventricular contractions, left ventricular hypertrophy and non-specific ST and T wave changes were seen on electrocardiography.

ECHOCARDIOGRAM

Echocardiography showed a normal ventricular function with an ejection fraction of 79%, aortic sclerosis, aortic valve area of 2 cm, and left ventricular hypertrophy.

LABORATORY

Hemoglobin was 13.5 g/dL, potassium 3.3 mmol/L, creatinine 1.5 mg/dL, and sodium 138 mmol/L.

IMAGING STUDIES

Magnetic resonance imaging revealed a large right adrenal mass measuring 1.8 cm x 8 cm. Central necrosis displaced the right renal vascular pedicles and right kidney inferiorly (figure 1). Consultation with a cardiologist was sought who recommended using perioperative beta-blockers.



Figure 1. Magnetic resonance imaging of a 1.8 cm x 8 cm right adrenal pheochromocytoma with central necrosis indicated by the arrows.

Intraoperative course

In the preoperative area the blood pressure of the patient was 180/105 mm Hg. The patient stated that the daily dose of anti-hypertensive medication had not been taken that day. The usual dose of amlodipine besylate, enalapril and labetalol were given with a sip of water. The patient was observed for approximately 2 hours. The patient was a little sweaty and had a slight tremor, but stated that this was normal for him.

A right radial arterial line and a right internal jugular two lumen central line were inserted. Before going to the operating room the blood pressure had declined to 160/95 mm Hg with a pulse rate of 90. In the operating room, ASA standard monitors were connected, and the patient was pre-oxygenated with 100% oxygen by mask, followed by intravenous induction of anesthesia using fentanyl (100 µg), lidocaine (100 mg), propofol (200 mg), and rocuronium (60 mg). Mask ventilation was easy.

Before attempting direct laryngoscopy for tracheal intubation, the blood pressure started to rise rapidly, 200 mm Hg range for systolic and 110 mm Hg for diastolic. The anesthesia depth was increased by raising the minimum alveolar concentration of isoflurane along with additional propofol (100 mg), fentanyl (150 µg) and esmolol (50 mg). The blood pressure continued to rise reaching the 300 mm Hg range for systolic and 150 mm Hg for diastolic. The patient was maintained on mask ventilation to avoid further stimulation by intubation.

A drip was started containing nitroglycerin (1 µg/kg/min) and nitroprusside (3 µg/kg/min), boluses of nitroglycerin (100 µg) and labetalol (100 mg) were given with no response. A bolus of 5 mg phentolamine was administered upon suspicion of the presence of pheochromocytoma. The blood pressure dropped within 2 minutes to nearly baseline levels (180/95 mm Hg). Surgery was canceled, the patient was intubated and sent to the intensive care unit for close monitoring and titration of a phentolamine drip. A few hours later the patient was extubated.

Postoperative Course

Within the first 24 hours, the creatinine levels of the patient increased to 2.5 mg/dL and cardiac troponin I increased to 6.3 ng/mL. As a result, the patient underwent angioplasty of an 80% stenosis of the circumflex branch. Upon discharge from the intensive care unit oral phenoxybenzamine was started to replace the intravenous phentolamine and the creatinine levels came back to baseline.

The patient went home with oral phenoxybenzamine. The diagnosis of pheochromocytoma was confirmed with the following laboratory data:

- 24 hour urine: normetanephrine 25,373 µg/mL (normal 50-840), metanephrine 669 µg/mL (normal 0-370), vanillylmandelic acid 155 µg/mL (normal <7.2), norepinephrine 5,297 µg/mL (normal 13-107), and epinephrine 47 µg/mL (normal 0-15).
- Plasma levels: norepinephrine 140,595 µg/mL (normal 200-1,700) and dopamine 266 µg/mL (normal <30).

Follow-up Adrenalectomy

Three weeks later the patient returned to the hospital for excision of the tumor. This time induction of anesthesia was uneventful as a consequence of adequate alpha-blockade. After excision of the tumor, the patient developed severe hypotension secondary to catecholamine depletion. Subsequent inability to compensate for surgical bleeding required multiple blood transfusions and vasopressors. The postoperative course was unremarkable. The patient was discharged 3 days later. The final pathologic report confirmed the presence of a malignant pheochromocytoma.

DISCUSSION

Based on this particular case, despite its low incidence, a diagnostic workup to rule out pheochromocytoma is warranted for every adrenal mass before the patient is sent to surgery. In the event of an anesthetic-induced hypertensive crisis, even potent antihypertensives, such as nitroprusside, may be ineffective. Phentolamine, however, proved effective. Phentolamine should be the treatment of choice for pheochromocytoma-related hypertensive crises.

Clinical suspicion remains the single most important factor in the identification of pheochromocytoma. In retrospect, this patient's history of labile hypertension and his tremor were likely manifestations of excess catecholamines secreted by the tumor. Adequate preoperative diagnosis of pheochromocytoma is based on both imaging and biochemical tests (table 1). Diagnostic laboratory tests have traditionally included 24 hour urinary metanephrine and vanillylmandelic acid levels. In addition, a clonidine suppression test will rule out any other cause for an increase of catecholamines. Catecholamine secretion from a pheochromocytoma is

Table 1. Diagnostic tests for pheochromocytoma.

	Sensitivity	Specificity	Reference
Imaging criteria			
Magnetic resonance	100%		2
¹³¹ I-MIBG scintigraphy	100%		2
Computed tomography	88%		2
Ultrasound	83%		2
Biochemical criteria			
Plasma			
Free metanephrines	99%	89%	3
Catecholamines	84%	81%	3
Urine			
Fractionated metanephrines	97%	69%	3
Catecholamines	86%	88%	3
Total metanephrines	77%	93%	3
Vanillylmandelic acid	64%	95%	3

MIBG = metaiodobenzylguanidine

independent of neurogenic control and therefore will not be suppressed by clonidine. Plasma-free metanephrine levels have proven to provide the best test for excluding or confirming pheochromocytoma, and should be the test of first choice for diagnosis of the tumor.³

Extirpation of the tumor is curative in 90% of the cases.⁴ Pheochromocytomas are bilateral in 10% of the cases; 10% are extra-adrenal, and 10% are malignant. The size of the tumor does not correlate with the severity of the symptoms.^{5,6} Laparoscopic adrenalectomy for pheochromocytoma has proven to be effective and to decrease recovery time, but overall outcome is the same as open surgery.⁷

Patients with pheochromocytoma are chronically vasoconstricted as a result of the high levels of circulating catecholamines and have a secondary decrease in their blood volume. Preparation for surgery should begin at least 2 weeks prior to allow full alpha-blockade along with gradual restoration of blood volume.⁸ A standard protocol for adrenergic blockade is to administer phenoxybenzamine, starting at a dose of 40 mg per day and gradually increasing to 80 to 120 mg per day. This single precaution may decrease perioperative mortality from 45% to 3%.¹ The most common side effect of phenoxybenzamine is postural hypotension.⁹ Beta-blockade can be given after starting alpha-blockade, if tachycardia or other cardiac arrhythmias develop.¹⁰ Beta-blockers must never be started prior to adequate alpha-blockade, since in the absence of beta-2-mediated vasodilation, profound unopposed alpha-mediated vasoconstriction may lead to hypertensive crisis or pulmonary edema.

To help assess the adequacy of preoperative management of pheochromocytoma, the following Roizen criteria¹¹ should be met in order to reduce perioperative morbidity and mortality:

- No in-hospital blood pressure >160/90 mm Hg for 24 hours prior to surgery.
- No orthostatic hypotension with blood pressure <80/45 mm Hg.
- No ST or T wave changes for 1 week prior to surgery.
- No more than 5 premature ventricular contractions per minute.

Calcium channel antagonists, like nicardipine, have also been shown to control hemodynamic response during resection of pheochromocytomas.⁷ Fenoldopam, a dopamine-like D1 receptor agonist, has been used to help lower blood pressure in patients with decreased renal function. However, fenoldopam is not effective as a single medication.

Another important factor in the management of these cases is the appropriate selection of preoperative medications. The patient must receive adequate anxiolytic medication in the immediate preoperative period. The muscle relaxant, pancuronium, has sympathomimetic properties, and therefore its use is contraindicated. Prazosin and magnesium are also used. Continuous infusion of magnesium (keeping

plasma levels <2 µg/mL to avoid potentiation with muscle relaxation) reduces catecholamine levels, blunts the response to intubation, and effectively controls blood pressure.^{1,9} Postoperative administration of inotropic agents concomitant with the administration of intravenous fluids are necessary to correct hypotension due to catecholamine withdrawal and intraoperative blood loss.

CONCLUSION

The management of patients with pheochromocytoma remains a challenge for the anesthesiologist despite the advent of new drugs and techniques. Treating patients preoperatively with alpha-adrenergic blockade is helpful for reducing intraoperative hypertensive episodes, thus decreasing morbidity and mortality.

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