Laparoscopic Bilateral Pheochromocytoma Resection in an Obese Teen with von Hippel-Lindau disease

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Objectives:

1. Describe the biochemical and physiologic features of pheochromocytoma and paraganglioma.

2. Identify current diagnostic and therapeutic trends for pheochromocytoma and paraganglioma.

3. Describe an appropriate preoperative preparation for surgery, and assess the patient’s readiness to proceed.

4. Design an anesthetic plan, based on the patient’s physiologic profile, from among the appropriate management options. Respond to intraoperative challenges, and adjust postoperative care accordingly.

Stem Case:

A 16 year old, 118 kg (BMI 36) male with bilateral pheochromocytomas is scheduled for a laparoscopic bilateral pheochromocytoma resection. He has von Hippel-Lindau disease, and had a laparoscopic cortical-sparing adrenalectomy of a left pheochromocytoma four years ago. A recent screen for plasma metanephrines revealed a large increase in plasma normetanephrines and total metanephrines. His MIBG scan revealed a new region of uptake in the right adrenal gland. A follow up CT scan confirmed the right adrenal lesion as well as a smaller left adrenal lesion and a lesion in the pancreas of unclear etiology.
• What is a pheochromocytoma? What is a paraganglioma? Is the distinction between them clinically relevant? Which familial disorders are typically associated with pheochromocytomas and paragangliomas? Clinical importance?
• Does the clinical presentation of pheochromocytoma and paraganglioma differ between the adult versus the pediatric population? What are common presenting symptoms of pheochromocytoma and paraganglioma in the pediatric population?
• How is the diagnosis of pheochromocytoma made? What are the preferred biochemical tests or testing algorithms for confirming or excluding the presence of a tumor? What evidence for the presence of a tumor justifies imaging studies? What imaging strategies are recommended? Role of newer functional imaging modalities (PET imaging, octreoscan)?
• Should all patients with pheochromocytomas or paragangliomas undergo genetic testing for possible disease-causing gene mutations or should this be confined to selected patients?
• What treatment options are available for these patients? What different surgical approaches exist? When is an adrenal cortex sparing procedure indicated?

The patient is admitted 3 days prior to the scheduled procedure. He was started on phenoxybenzamine 3 weeks ago, as well as metyrosine 2 weeks ago, both with escalating doses to the current phenoxybenzamine 30mg four times a day and metyrosine 750mg four times a day. He has been on a high volume (>3 liters/day) and high sodium diet (>5 grams/day). He has complained of orthostatic symptoms and significant nasal congestion. He denies chest pain, flushing, diaphoresis, and palpitations. His current vital signs are: T 36.7C, pulse 92, BP 135/68, RR 18, Sat 99% on room air.

• What are your goals for the preoperative management of patients with pheochromocytoma/paraganglioma? When should preoperative preparation be started? What clinical parameters should be monitored?
• What pharmacological agents are preferred for the management of preoperative hypertension? What is the role of phenoxybenzamine (dosing, side effects, cost)? When are beta adrenoceptor antagonists, combined alpha and beta adrenoceptor antagonists, and/or calcium channel blockers indicated?
• Why is this patient receiving metyrosine (dosing, side effects, cost)? Should it be used preoperatively in all patients?
• Are the levels of plasma or urine metanephrines and normetanephrines helpful during the preoperative preparation phase?
• Why are these patients placed on a high volume, high sodium diet?
• What criteria do you use to decide that the patient is ready for surgery? What other labs and studies would you require?
On the day of surgery, the patient’s vitals signs are: T 36.8C, pulse 95, BP 140/72, RR 20, Sat 99% on room air. Are these values optimized? Are you willing to proceed? He appears mildly anxious. During his 3-day admission, he was continued on phenoxybenzamine and metyrosine, as well as a high volume and high salt diet. Overnight, he received a continuous infusion of normal saline. In the holding area, the nurse states that his peripheral IV is infiltrated and nonfunctional.

- Would you premedicate this patient for his anxiety? If so, how?
- How do you plan to induce anesthesia? IV induction versus inhalational induction? Are there special airway concerns related to this patient’s obesity? Specific concerns regarding induction agents and neuromuscular blocking agents in the patient with pheochromocytoma? Available techniques that may attenuate the hemodynamic response to laryngoscopy and intubation?
- Is invasive hemodynamic monitoring indicated? Do you think a CVP is required for this laparoscopic case? When would a pulmonary arterial catheter or intraoperative echocardiography be indicated?
- What maintenance technique would you select for this patient? Why? Is desflurane a reasonable option? Dexmedetomidine?
- How do you plan to manage this patient’s intraoperative/postoperative pain? Is morphine a reasonable option, with a PCA for postoperative pain? Would you consider placement of an epidural catheter? If so, when? Awake or asleep?
- Would you employ epidural analgesia intraoperatively, or reserve it for the postoperative period?

The patient is anesthetized. Surgical incision is uneventful. Following insufflation of the abdomen, the patient’s blood pressure increases to 200/120.

- When might you expect to see intraoperative hypertension?
- Are there special concerns related to laparoscopy in this obese patient?

Once the tumors are located, it becomes necessary to open the abdomen with a wide chevron incision; additional masses, possibly paragangliomas, are found. Blood loss is considerable. After the venous supply to the first pheochromocytoma is ligated, the blood pressure decreases to 60/40.

- Would you expect to see intraoperative hypotension? When? What are the possible etiologies?
• How would you manage his hypotension? Fluids? Pressors? Which? What if he did not respond to your first choice? How well do these patients respond to routine vaspressors? Would you consider the use of vasopressin in this scenario?

The surgical procedure lasts 10 hours. The final surgical procedure includes: bilateral adrenalectomies, excision of a right retrocaval mass and excision of a right suprarenal mass. The patient is currently hemodynamically stable on a low dose vasopressin infusion. During the case, he received 9 liters of Plasma-Lyte, 500 milliliters of 5% albumin, and 2 units of packed red blood cells.

• Would you plan to extubate this patient at the end of the procedure?
• What hemodynamic changes do you anticipate postoperatively? How would you address persistent hypertension? How would you address persistent hypotension?
• Do you have special concerns related to this patient’s blood glucose management? Adrenal insufficiency? Plans for long-term steroid replacement?
• How would you plan to manage his postoperative pain? Which analgesic adjuncts might you consider?

The patient does well postoperatively, and he is discharged home after 4 days. Following his discharge home, the final surgical pathology report reads: right retrocaval mass (extra-adrenal paraganglioma), right suprarenal mass (extra-adrenal paraganglioma), right adrenal gland (pheochromocytoma), and left adrenal gland (pheochromocytoma).

• What is the appropriate follow-up of patients after surgical resection of a tumor?
• What are the outcomes regarding diagnosis and treatment of pheochromocytomas and paragangliomas in children?
**Model Discussion:**

In 2004, the World Health Organization classification of endocrine tumors defined a pheochromocytoma as a tumor arising from catecholamine-producing chromaffin cells in the adrenal medulla, an intra-adrenal paraganglioma. Closely related tumors of extra-adrenal sympathetic or parasympathetic paraganglia are classified as extra-adrenal paragangliomas. Because these tumors can have similar presentations and are treated with similar clinical approaches, many clinicians may use the term "pheochromocytoma" to refer to both intra-adrenal pheochromocytomas and extra-adrenal paragangliomas. However, the distinctions between the two entities are important as they relate to associated neoplasms, risk for malignancy, and genetic testing.

Pheochromocytomas and paragangliomas are rare neoplasms, and they are rare causes of hypertension in adults and children. In the adult population, catecholamine-secreting tumors typically present in the 4th to 5th decade of life and occur in less than 0.2 percent of patients with sustained hypertension. In adult patients, most of these neoplasms present sporadically, whereas 15-20% are associated with a familial disorder. In the pediatric population, catecholamine-secreting tumors typically present around ages 11-12 and occur in 0.8 to 1.7% of hypertensive children. Thirty to forty percent of children diagnosed with pheochromocytoma/paraganglioma have an associated familial disorder.

Several familial disorders are associated with pheochromocytoma, all of which have autosomal dominant inheritance: von Hippel-Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), and less commonly, neurofibromatosis type 1. The frequency of pheochromocytoma in these disorders is 10-20 percent in VHL, 50 percent in MEN2, and 0.1 to 5.7 percent in neurofibromatosis type 1. Von Hippel-Lindau disease and neurofibromatosis type 1 are rarely associated with paragangliomas. Familial paraganglioma is an autosomal dominant disorder characterized by paragangliomas; this disorder is most commonly caused by mutations in the succinate dehydrogenase subunit genes (SDH), and is frequently associated with metastatic disease. The VHL phenotype includes pheochromocytoma (frequently bilateral, increase serum concentration of normetanephrine), rarely paraganglioma, retinal angiomas, cerebellar hemangioblastoma, epididymal cystadenoma, renal and pancreatic cysts, pancreatic neuroendocrine tumors, and renal cell carcinoma. The MEN2A phenotype includes pheochromocytoma (frequently bilateral, increase serum concentration of metanephrine), medullary thyroid carcinoma, and primary parathyroid hyperplasia. MEN2B represents 5 percent of MEN2 cases and the phenotype includes pheochromocytoma (frequently bilateral), medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, intestinal ganglioneuromatosis, and marfanoid body habitus.
The signs and symptoms related to pheochromocytomas and paragangliomas are caused by tumor hypersecretion of catecholamines: norepinephrine, epinephrine, and dopamine. The “classic triad” of episodic headache, sweating, tachycardia and HTN is traditionally described in the adult population, however, only fifty percent of adults with pheochromocytoma have one or more of these classic symptoms. Other signs and symptoms that may be associated with pheochromocytoma and paraganglioma include: pallor, visual blurring, orthostatic hypotension, weight loss, polyuria/polydipsia, hyperglycemia, and cardiomyopathy. A retrospective review of 30 pediatric patients with pheochromocytoma and paraganglioma showed common presenting symptoms as hypertension (64%), palpitations (53%), headaches (47%), and mass-related effects (30%).

Diagnostic options for pheochromocytoma and paraganglioma have changed considerably in the past two decades. Catecholamines are metabolized within chromaffin cells to metanephrines (epinephrine to metanephrine and norepinephrine to normetanephrine); studies have confirmed that measurements of fractionated metanephrines in urine (24-hour collection) or plasma provide superior diagnostic sensitivity over measurements of parent catecholamines. There is no consensus on whether plasma or urine measurements are superior. In the young pediatric patient in whom a 24-hour collection is not possible, measurement of plasma fractionated metanephrines is a reasonable initial test. This is a relatively newer test that is becoming increasingly available. Measurement of plasma or urine catecholamines and metabolites are highly sensitive and specific in pediatric patients with symptoms. Other tests that have been described in adult patients with pheochromocytoma such as the clonidine suppression test and glucagon stimulation test have not been validated in studies of children with suspected pheochromocytoma.

Localization of a pheochromocytoma or paraganglioma should be considered if the clinical evidence for the presence of a tumor is reasonably compelling. Either computed tomography (CT) or magnetic resonance imaging (MRI) is recommended for initial tumor localization. Adrenergic blockade as a precautionary measure prior to administration of intravenous contrast is not necessary with current contrast agents. The higher specificity of functional imaging such as 123-I-metaiodobenzylguanidine (MIBG) imaging may be useful to detect tumors not detected by CT or MRI. MIBG imaging may also be useful to further evaluate disease extent and presence of multiple tumors or metastases. Positive emission tomography (PET) scanning with 18F-fluorodeoxyglucose or 11C-hydroxyephedrine or 6-[18F]fluorodopamine is a newer radionuclide localization technique which in recent studies demonstrates superiority to MIBG in detection of metastases. OctreoScan is another functional imaging modality that, like PET scanning, should be reserved for patients with negative MIBG imaging or rapidly growing tumors.
Genetic testing should be considered if a patient has: bilateral adrenal pheochromocytoma, paraganglioma, presentation at a young age, family history of pheochromocytoma/paraganglioma, or clinical findings suggestive of an associated familial disorder. Mutation testing is routinely available for the genes associated with VHL, MEN2, neurofibromatosis type 1, and familial paraganglioma.

Once a pheochromocytoma or paraganglioma is diagnosed, a patient should undergo surgical resection after appropriate medical preparation. Complete surgical resection remains the only curative therapy for pheochromocytoma. Although open surgical approaches to treat pheochromocytoma have been used since the 1920's, laparoscopic adrenalectomies have been shown to be safe and advantageous. Laparoscopic resections have been performed in cases of unilateral or bilateral lesions, as well as extra-adrenal lesions. These procedures have been described mostly in case reports and case series in the pediatric literature. An adrenal cortex-sparing approach has been advocated in some patients with hereditary forms of primary or recurrent pheochromocytoma, thereby avoiding or postponing permanent adrenal insufficiency; the risk of this approach is recurrent pheochromocytoma.

Although proper and adequate preoperative preparation is essential for the anesthetic management of pheochromocytoma, no universally accepted method of preparation for surgery in children with pheochromocytoma has been established. The length of preoperative therapy also remains controversial with several studies noting conflicting results. Overall goals of preoperative management include: normalization of blood pressure and heart rate, control of secondary symptoms, expansion of the contracted blood volume, and decreasing tumor catecholamine synthesis. The mainstay of preoperative treatment of hypertension has been via alpha-adrenoceptor antagonists. The alpha-adrenoceptor antagonist most commonly used and recommended is phenoxybenzamine, an irreversible noncompetitive alpha-adrenoceptor blocker. The starting dose of phenoxybenzamine in children is 0.25 to 1 mg/kg per day; the dose is increased every few days until the patient's symptoms and blood pressure are controlled and mild orthostasis has been induced. Dosing of phenoxybenzamine may be limited by intolerance of side effects including: postural hypotension with reflex tachycardia, dizziness, syncope, and nasal congestion. Determination of adequate blood pressure control may be difficult to assess. Some authors suggest titrating phenoxybenzamine until the child's blood pressure is normal for age and height. In adults, adequate alpha-blockade is suggested to be indicated by the Roizen criteria: a blood pressure less than 160/90 mmHg, orthostatic hypotension, ST segment resolution on EKG, and infrequent premature ventricular contractions. Specific, competitive, short acting alpha-one adrenergic antagonists such as prazosin, terazosin, and doxazosin have also been used as alternatives to phenoxybenzamine. Dosing increases and titration of these agents is achieved more quickly and with less side effects compared with phenoxybenzamine, however, reports of perioperative blood pressure control with these agents compared with phenoxybenzamine show conflicting results. Patients are typically started on a normal or high salt diet 2 to 3
days after alpha-adrenergic blockade is initiated in order to improve postural hypotension and normalize a reduced blood volume secondary to chronic vasoconstriction.

Following adequate alpha-adrenergic blockage, beta-adrenergic blockade may be initiated to treat catecholamine or alpha blocker induced tachyarrhythmias. Beta-adrenergic blockade should only be initiated in the presence of established alpha-adrenergic blockade. Blockade of vasodilatory peripheral beta-adrenergic receptors with unopposed alpha-adrenergic receptor stimulation can lead to further increases in blood pressure. Combined alpha and beta adrenoceptor antagonists such as labetalol should not be used as the primary choice for alpha-blockade since its beta-antagonist effects predominate over any alpha-antagonist effects it possesses.

Calcium channel blockers can be used as a supplement to adrenoceptor blockade, or they can be used to replace adrenoceptor blockers in patients who experience severe side effects. A 2005 review of 65 adult patients showed that the sole use of nicardipine preoperatively for pheochromocytoma or paraganglioma resection did not prevent all intraoperative hemodynamic changes, however, its use was associated with a low morbidity and mortality.

Another approach in the preoperative preparation of children undergoing pheochromocytoma or paraganglioma resection is the administration of metyrosine, a catecholamine synthesis inhibitor. Metyrosine competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis, decreasing tumor catecholamine stores. In conjunction with alpha-blockade, the use of metyrosine may facilitate better perioperative hemodynamic control. Treatment with metyrosine is typically started 1 to 3 weeks before surgery, however, increased dosing may be limited to side effects including: sedation, depression, anxiety, extrapyramidal signs (rare), and diarrhea and crystalluria at high doses. Some centers advocate the routine preoperative use metyrosine, however, many centers reserve it for patients who cannot be treated with traditional adrenergic blockade.

A detailed history, physical examination, and a complete laboratory evaluation are essential in preparing the patient with pheochromocytoma or paraganglioma for surgery. A full search for any evidence of cardiac dysfunction should be performed preoperatively, as chronic exposure to high levels of catecholamines may lead to catecholamine induced cardiomyopathy. The value of preoperative echocardiography in patients without cardiac symptoms or clinical evidence of cardiac involvement is controversial.

Various anesthetic techniques have been used in the resection of pheochromocytoma and paraganglioma in both children and adults. The key points are that the anesthesiologist chooses an anesthetic plan with which they are most experienced, and that close communication with the surgical team is maintained throughout the procedure. In addition to standard monitoring, an intra-arterial
catheter for pressure monitoring is essential for immediate identification of hemodynamic fluctuations. Central venous catheter placement for infusion and monitoring is commonly used and recommended. The use of pulmonary artery catheters in pediatric patients is uncommon, however, if significant myocardial dysfunction is present or anticipated, use of these catheters may help prevent occurrence of perioperative cardiovascular complications. The use of transesophageal echocardiography has been described mostly in adults undergoing pheochromocytoma resection.

Prior to tumor removal, various stimuli can precipitate excess catecholamine release including: induction, intubation, positioning, surgical incision, creation of pneumoperitoneum in laparoscopic procedures, and tumor manipulation. During these unstable periods plasma catecholamine levels may reach several hundred times normal levels. Almost all of the commonly used induction agents and neuromuscular blocking agents have been used with success. Succinylcholine may increase blood pressure by stimulation of autonomic ganglia or by mechanical stimulation of the tumor by fasciculations; however, its safe use has been shown in patients undergoing pheochromocytoma resection. Pharmacological agents associated with histamine release such as atracurium and morphine theoretically may increase blood pressure and elevate plasma catecholamine levels, but these agents have also been safely used in clinical practice. Various techniques known to attenuate the hemodynamic response to laryngoscopy and intubation have been described including: intravenous lidocaine, high dose opioids, esmolol, labetalol, and magnesium sulfate. Almost every agent has been described in the maintenance of anesthesia; little evidence exists to suggest that any one method or drug is clearly better than another. Isoflurane and sevoflurane have been used safely in children undergoing pheochromocytoma resection. The safe use of desflurane has been described in some case reports, including the use of desflurane with remifentanil in a pediatric patient undergoing bilateral pheochromocytoma resection. Dexmedetomidine has also been described as an anesthetic adjunct in some case reports (one pediatric); as an alpha-2 agonist, it may improve intraoperative hemodynamics and reduce the release of catecholamines in patients undergoing pheochromocytoma resection. Intravenous opioids are often used for analgesia; the use of epidural analgesia has been described in adults as well as pediatric patients with satisfactory results. Epidural analgesia may blunt the sympathetic response to surgical incision, however, it does not protect against catecholamine release during tumor manipulation.

Numerous case series and case reports have described the use of various antihypertensive agents during pheochromocytoma and paraganglioma resection. Sodium nitroprusside is a short-acting direct vasodilator that is frequently used to control intraoperative hypertension. Phentolamine is a competitive alpha-one adrenergic and weak alpha-two adrenergic receptor antagonist that can be given intravenously or as an infusion to control intraoperative hypertension. Compared to sodium nitroprusside, its action can be long lasting and unwanted reflex tachycardia can be produced. Esmolol, a short acting beta one antagonist has
bilateral adrenalectomy is necessary, glucocorticoid coverage should be initiated. The patient should receive glucocorticoid stress coverage preoperatively; if unexpected bilateral adrenalectomy is necessary, glucocorticoid coverage should be initiated.

Following adrenal vein clamping and tumor isolation, profound hypotension may ensue. Persistent hypotension might also be related to inadequate intravascular volume, residual effects of preoperative alpha-adrenergic blockade, abrupt decrease in catecholamine levels, loss of tonic vasoconstriction, and hemorrhage. Fluids should be administered first and should be guided by information from a central venous catheter in order to avoid hypervolemia. The use of vasopressors may be required to maintain adequate mean arterial pressure: norepinephrine, epinephrine, phenylephrine, and dopamine have all been recommended. Recent case reports have demonstrated vasopressin to be effective in treating refractory hypotension following pheochromocytoma excision. Patients with catecholamine secreting tumors may have decreased vasopressin levels secondary to excessive catecholamine levels, which may inhibit vasopressin release. Deutsch and Tobias (2006) describe the effective use of vasopressin (5 units, then 0.5mU/kg/min to 3mU/kg/min) to treat hypotension refractory to fluids, phenylephrine, and norepinephrine following the resection of a pheochromocytoma in an eleven year old boy. Similar case reports have been described in the adult literature.

Postoperatively, the patient should be transferred to a suitable postoperative care unit. Analgesia can be provided with either epidural analgesia or intravenous opioids. Some patients may remain temporarily hypertensive postoperatively, likely related to elevated catecholamine stores in adrenergic nerve endings. Other causes of persistent hypertension include fluid excess, presence of residual tumor, or inadvertent ligation of a renal artery. The majority of patients will likely experience persistent hypotension related to preexisting hypovolemia, alteration of vascular compliance, fluid losses from bleeding or third spacing, or residual effects of preoperative adrenergic blockade. In patients who undergo bilateral adrenalectomies, long-term steroid replacement therapy is required and endocrinology should be consulted. If bilaterally adrenalectomy is planned, the patient should receive glucocorticoid stress coverage preoperatively; if unexpected bilateral adrenalectomy is necessary, glucocorticoid coverage should be initiated.
intraoperatively. Adrenal insufficiency may contribute to perioperative hypotension. Postoperative glucose monitoring is recommended in patients following pheochromocytoma or paraganglioma resection due to concerns related to hypoglycemia. Decrease in circulating catecholamine levels following tumor resection, increased insulin secretion, and effects of beta-adrenergic blockade may contribute to postoperative hypoglycemia.

Long term periodic follow up is recommended for all cases of pheochromocytoma and paraganglioma, even those apparently cured. In one report of 14 children treated over a 36-year period (Hospital for Sick Children), four (28%) children had recurrences within 6 years. A retrospective chart review from Mayo Clinic covering a 30-year period showed a higher incidence of malignancy among children with pheochromocytoma or paraganglioma (47%) compared with typical adult malignancy rates. However, their 5-year disease-specific survival rate (90%) was more favorable than that for adults. At our institution, a report of 15 children treated over a 38-year period showed a low rate of malignancy (7%), with a 100% overall survival and 93% five-year disease free survival.
References:


