

Metastatic Pheochromocytoma in an Asymptomatic 12-Year-Old With von Hippel-Lindau Disease

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Pheochromocytoma is a rare chromaffin cell tumor that may be associated with a genetic predisposition, such as von Hippel-Lindau (VHL) disease. VHL is an autosomal dominant disorder that is characterized by a predisposition to multiple tumors, including retinal and central nervous system hemangioblastomas, renal cell carcinoma, and pheochromocytomas. The classic presentation of pheochromocytoma is episodic hypertension, headaches, palpitations, and diaphoresis. In the pediatric population, 40% of pheochromocytomas have a hereditary basis. We present a case of metastatic pheochromocytoma in a child with VHL and discuss the relevant current medical literature. UROLOGY ■■: ■■–■■, 2018. © 2018 Elsevier Inc.

Pheochromocytoma is a rare chromaffin cell tumor that may be associated with a genetic predisposition, such as von Hippel-Lindau (VHL) disease.¹ VHL is an autosomal dominant disorder that predisposes affected individuals to several tumors, pertinent for urologists, such as renal cell carcinoma and pheochromocytoma.² Approximately 40% of pediatric pheochromocytomas have a hereditary basis.³ Classic presentation of pheochromocytoma includes hypertension, headaches, palpitations, and diaphoresis. Pheochromocytoma can also be accompanied by syncope, anxiety, pallor, and nonspecific complaints, such as abdominal pain, blurred vision, and weight loss. The screening protocol for pheochromocytoma in VHL is annual serum metanephrines and catecholamines beginning at age 5 years.⁴

CASE PRESENTATION

An asymptomatic 12-year-old boy with VHL was referred to urology for elevated plasma metanephrines. The patient had a history of a right thoracic paravertebral paraganglioma, resected at age 5. He had undergone screening plasma metanephrines and abdominal ultrasound every 3 months, central nervous system screening with magnetic resonance imaging every 2 years, and ophthalmology screening every 2 months. Family history was negative for VHL or any genitourinary malignancies.

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Physical examination at presentation revealed a blood pressure of 135/83 mm Hg and no abdominal masses. Laboratory findings were all within normal limits except for his plasma-free normetanephrine, which was elevated at 7 nmol/L. The abdominal ultrasound result was normal. Computerized tomography of the chest, the abdomen, and the pelvis showed bilateral suprarenal retroperitoneal masses (1.5 and 2.0 cm) and 3 peripheral lung nodules, all less than 5 mm in size (Fig. 1). Metaiodobenzylguanidine scan showed increased uptake by the 2 retroperitoneal masses, but the lung lesions were negative (likely below the size resolution of the scan) (Fig. 2).

An open bilateral retroperitoneal mass excision with right video-assisted thoracoscopic resection for 3 lung lesions was planned. Preoperative alpha-blockade with phenoxybenzamine and sodium chloride tabs was started 3 weeks preoperatively. A Chevron incision extended between the 12th ribs. A right interaortocaval mass was observed posterior and cranial to the left renal vein (Fig. 3). Further dissection behind the inferior vena cava revealed the mass was abutting the medial edge of the right adrenal gland, which was left in situ as the mass was then resected. We then moved to the left-sided tumor, exposing the left renal vein, the left adrenal vein, and the left adrenal gland. The mass was arising from the left adrenal gland, and a left partial adrenalectomy was performed. Video-assisted thoracoscopic resection of the lung lesions was then performed by pediatric surgery. The patient was transferred to the pediatric intensive care unit for monitoring postoperatively and was moved to the floor on postoperative day 1. He was discharged on postoperative day 5, with no complications.

Final pathology showed a 2.5-cm right lesion, 1.8-cm left lesion, and 3 lung specimens, all of which were positive for pheochromocytoma. All margins were negative. One

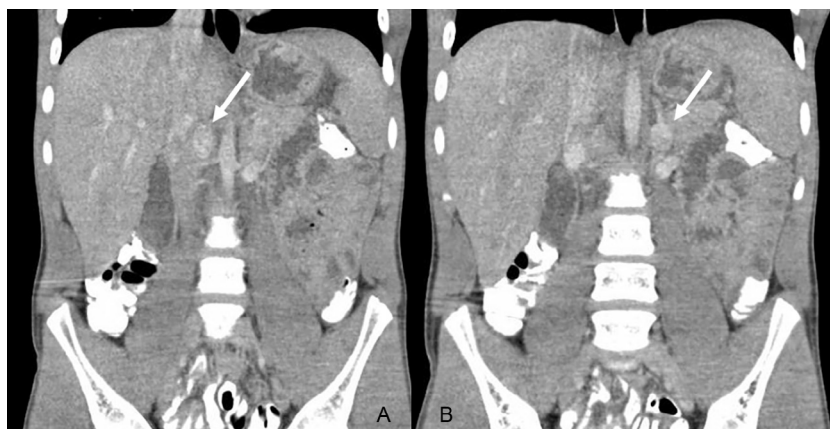


Figure 1. Computerized tomography imaging preoperatively demonstrates the interaortocaval mass (arrow) **(A)** and the left retroperitoneal mass (arrow) **(B)**.

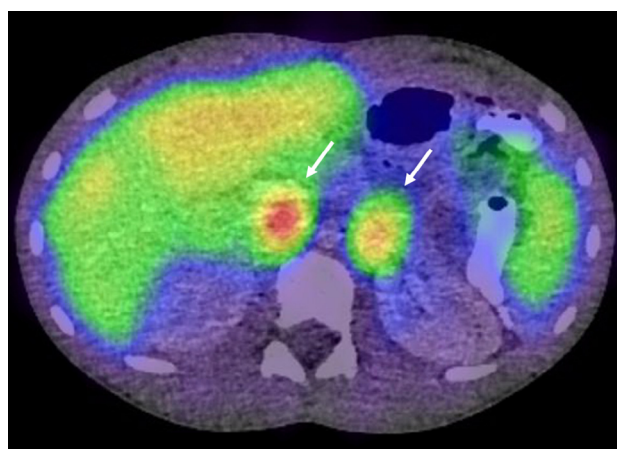


Figure 2. Metaiodobenzylguanidine scan shows 2 retroperitoneal masses (arrows) with avid metaiodobenzylguanidine uptake. (Color version available online.)

lymph node was negative for malignancy. Postoperative laboratory values returned to normal. As all disease had been resected, chemotherapy was not indicated. At the patient's 3-month follow-up, metanephrines continued to be within normal limits and imaging showed no recurrent disease.

DISCUSSION

VHL is a multisystem cancer predisposition syndrome that is associated with a mutation of the tumor suppressor VHL gene located on chromosome 3p.⁵ The inherited mutation causes individuals to have 1 normal gene (wild type) and 1 mutated gene. The Knudson 2-hit hypothesis states that this germline mutation is "first hit," and the individual must undergo a "second hit" before the development of a tumor. Tumors observed in individuals with VHL are cystic and vascular, throughout the body, including cerebellar, spinal, or retinal hemangioblastomas, renal cysts,

clear cell renal cell carcinomas, pheochromocytomas, pancreatic cysts, endolymphatic sac tumors, pancreatic neuroendocrine tumors, and epididymal and broad ligament cystadenomas.⁵

Pheochromocytoma is a neuroendocrine tumor characterized by the storage, synthesis, and release of catecholamines. The traditional "rule of tens" for pheochromocytoma suggests that 10% are malignant, 10% are extra-adrenal, 10% are extra-abdominal, 10% are not associated with hypertension, 10% are malignant, and 10% are hereditary.⁶ However, this rule is not perfect, with current estimates of genetic mutation associated pheochromocytomas sitting around 25% overall, but even higher (40%) in pediatric cases.^{6,7} Of patients with VHL, 10%-20% will develop a pheochromocytoma, typically as adults (mean age at presentation 30 years old).^{8,9} Symptomatically, children present like adults, with hypertension, palpitation, diaphoresis, headaches, pallor, syncope, nausea, and anxiety. Additionally, children tend to present with nonspecific symptoms, including blurred vision, abdominal pain, weight loss, hyperglycemia, polyuria, or polydipsia.¹⁰ However, in children and particularly in those with genetic syndromes, patients can be asymptomatic.¹ As this silent presentation is common, screening has become imperative in the detection of pheochromocytoma in patients with VHL, and is performed with annual serum or urine metanephrines and catecholamines, beginning at age 5 years.⁴ Laboratory testing is augmented with imaging, including computerized tomography or MRI for adrenal masses, whereas metaiodobenzylguanidine was commonly used for extra-adrenal masses.¹

The treatment of pheochromocytoma is surgical resection. Pharmacologic alpha-blockade in the preoperative period is essential to prevent catecholamine surge during induction of anesthesia or tumor manipulation. This could lead to hypertensive crisis, cardiomyopathy, pancreatitis, stroke, seizures, or multiorgan failure.¹⁰ If reflex tachycardia is a complication of the alpha-blockade, beta-blockers may be added.¹⁰

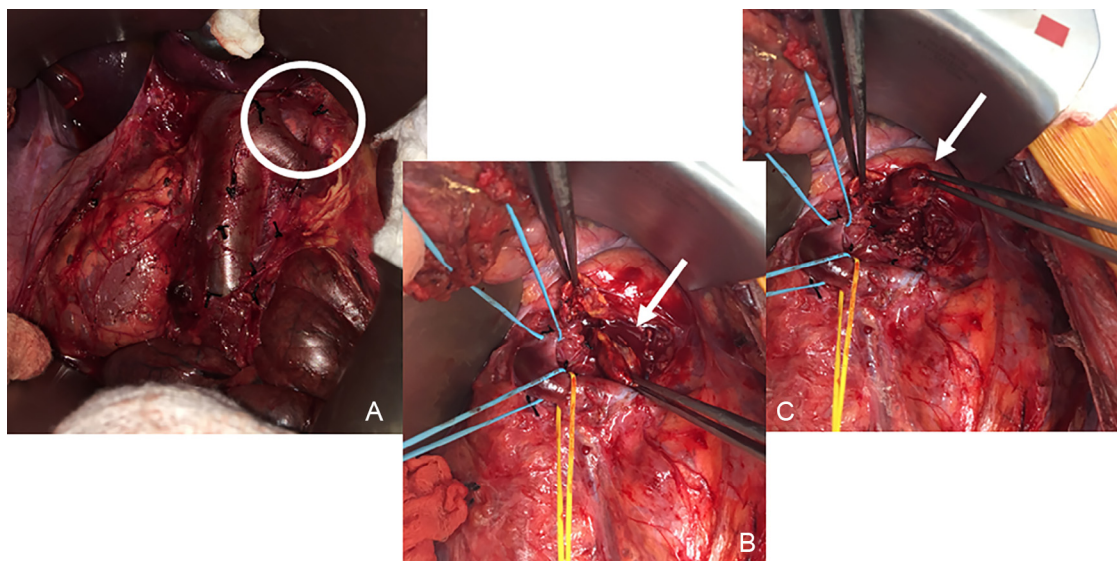


Figure 3. Postresection intraoperative image of the right interaortocaval mass (white circle) superior to the left renal vein (**A**). Left-sided mass (arrows) visualized arising from within the left adrenal gland (**B,C**). (Color version available online.)

In the pediatric population, approximately 12% of pheochromocytomas are malignant, with a 5-year survival of approximately 78%.¹⁰ A challenge lies in distinguishing malignant and benign pheochromocytomas as currently, there are no pathologic features or imaging characteristics that predict the malignant potential of this tumor—the presence of metastatic lesions is the only way to diagnose malignancy. Generally though, malignant tumors tend to have necrosis, a higher proliferative index, absent hyaline globules, extra-adrenal location, and size >5 cm.^{10,11}

The current recommended therapy for metastatic disease is surgical resection or all diseases. Radiation and chemotherapy can be used but only provides symptom relief and tumor regression in 50% of patients without any improvement in overall survival.¹¹ There have been reports of successful adjuvant treatment with ¹³¹I-labeled metaiodobenzylguanidine, with a response in 22% of adult patients, but further studies are needed.¹² Because metastasis can occur late in the clinical course, long-term follow-up with biochemical screening (urine or plasma metanephrines) and imaging studies is recommended.¹¹

CONCLUSION

For pediatric patients with VHL, pheochromocytoma commonly presents with either vague symptoms or none at all, making screening fundamental to its detection. Although metastasis is rare, it can occur in pediatric patients, and patients should be followed up long term with imaging and biochemical testing. At this time, surgical resection is the best treatment option for both local and metastatic pheochromocytomas.

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