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Case Report

Multiple Primary Paragangliomas in a Pediatric Patient With von Hippel Lindau: A Diagnostic Dilemma

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Abstract

Pheochromocytoma and paragangliomas (PPGLs) are rare chromaffin cell tumors arising from neural crest tissue. The majority of these tumors are nonmetastatic, with complete cure achieved through surgical resection. PPGLs have been associated with several hereditary cancer syndromes, including von Hippel-Lindau (VHL). We present the case of a 10-year-old patient with VHL and a history of 2 asynchronous pheochromocytomas requiring bilateral adrenalectomies who presented with a new 1.2 cm × 1.3 cm × 1.5 cm nodular structure between the superior pole of the right kidney and the intrahepatic inferior vena cava. The patient was noted to have hypertension but was otherwise asymptomatic. Positron emission tomography-DOTA-(Tyr)^3-octreotate revealed a metabolically active retrocrural lymph node. Based on these imaging findings and laboratory studies showing elevated plasma normetanephrine, clinical suspicion was highest for metastatic pheochromocytoma. The patient underwent surgical resection of multiple abdominal tumors. Pathology ultimately favored a diagnosis of multiple primary paragangliomas rather than metastatic disease. With this shift in diagnosis, the patient was managed with surgery alone. One year later, he has no signs of disease recurrence. Long-term surveillance imaging and screening with fractionated plasma metanephrines is indicated to monitor for new tumors in the setting of VHL and 3 prior endocrine tumors.

Key Words: paraganglioma, pheochromocytoma, von Hippel-Lindau

Introduction

Pheochromocytoma and paragangliomas (PPGLs) are rare chromaffin cell tumors arising from neural crest tissue. Pheochromocytomas arise from the adrenal medulla, whereas paragangliomas arise from extra-adrenal locations and are divided into sympathetic and parasympathetic (1-3). These tumors are rare, with an overall incidence of 2 to 8 per million persons per year (3). Most PPGL are localized, though 10% to 25% of individuals present with metastatic disease (4). Common presenting symptoms include hypertension, headache, palpitations, and perspiration, with pediatric patients more likely to have sustained hypertension (3). Diagnosis is made based on abdominal imaging with magnetic resonance imaging (MRI) or computed tomography scan, often in addition to elevated plasma free metanephrines (PFM) (1). As pathology is the gold standard for diagnostic confirmation, excisional biopsy is often performed, given the risk for inducing a hypertensive crisis with core biopsies (2).

Compared to the adult population, PPGLs in children are more often extra-adrenal, metastatic, and recurrent (5). Around 80% of pediatric PPGLs are related to an underlying cancer predisposition syndrome, and all patients diagnosed with PPGLs should be referred for genetic counseling (5). Hereditary cancer syndromes associated with the development of PPGLs include von Hippel Lindau (VHL), multiple endocrine neoplasia 2A and 2B, neurofibromatosis 1, and hereditary pheochromocytoma/paraganglioma syndrome, which involves pathogenic variants (PV) in the *SDHx* genes (3, 5). Based on data from the European-American Pheochromocytoma Paraganglioma Registry, 38% of patients diagnosed with an initial PPGL go on to develop a secondary tumor following initial resection. As expected, the recurrence rate is higher in patients with hereditary cancer syndromes, specifically associated with *VHL* and *SDHD* PV (6).

VHL is a rare, autosomal dominant cancer predisposition syndrome associated with a wide range of vascular tumors and cancers including retinal and central nervous system hemangioblastoma, renal cell carcinoma, PPGLs, endolymphatic sac tumors, renal and pancreatic cysts, pancreatic neuroendocrine tumors, and broad ligament and epididymal cystadenomas (7-9). PPGLs will occur in 10% to 20% of patients with VHL (9). Thus, routine surveillance screening for early detection is recommended for all patients with VHL. According to the American Association for Cancer Research Consensus Guidelines, annual screening with PFM is recommended starting at age 2. In addition, annual MRI of the abdomen is recommended starting at age 10 to screen for adrenal tumors and pancreatic neuroendocrine tumors. An MRI of the brain and spine is recommend biennially starting at age 8 to screen for central nervous system hemangioblastoma (9).

Here we report an interesting and diagnostically challenging case of a patient with VHL type 2A and a history of bilateral

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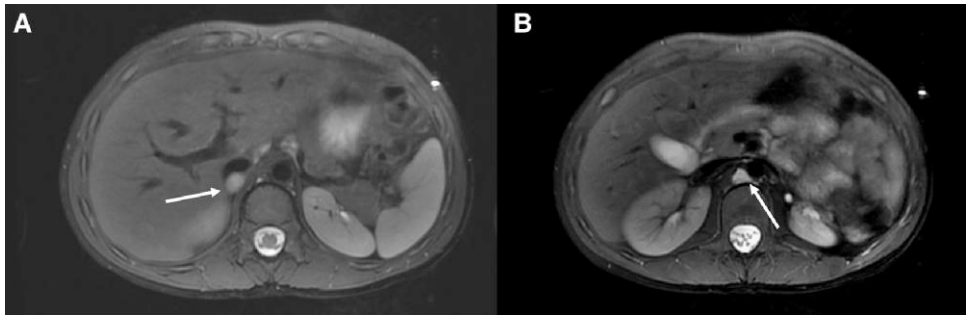

Figure 1. Magnetic resonance imaging abdomen with intravenous contrast reveals a 1.2 cm × 1.3 cm × 1.5 cm nodular structure between the superior pole of the right kidney and the intrahepatic inferior vena cava (A). The presence of an enlarging retrocrural lymph node (B) raises suspicion for metastatic disease.

pheochromocytoma found to have a new tumor on MRI between the superior pole of the right kidney and intrahepatic inferior vena cava, with a metabolically active retrocrural lymph node (Fig. 1). These imaging findings were initially most concerning for metastatic pheochromocytoma. However, pathology revealed multiple primary paragangliomas as the final diagnosis in this case.

Case Presentation

The patient is a now 10-year-old male who had initially presented to care at age 4 with headache and hypertension. He was diagnosed at that time with a left-sided pheochromocytoma based on computed tomography of the abdomen with intravenous contrast as well as elevated PFM. He underwent left adrenalectomy for surgical management of his tumor. There is a history of VHL on the paternal side of the family, and genetic testing for the patient at the time of initial presentation confirmed a known familial pathogenic variant (c.292T>C/p.Y98H) in exon 1 of the *VHL* gene.

Given the diagnosis of VHL, type 2A, he continued with regular abdominal imaging and PFM annually. Four years later (age 8), he was noted to have a new right-sided adrenal mass on screening abdominal ultrasound. He underwent resection of the mass and partial right adrenalectomy, with pathology confirming a diagnosis of a new pheochromocytoma. He developed surgical adrenal insufficiency following this second resection and has been maintained on scheduled hydrocortisone since that time.

Two years later (age 10), he presented to clinic for a routine follow-up visit accompanied by a surveillance MRI. The patient and his family reported no concerns or new symptoms at the time. He denied any visual changes, headaches, or abdominal pain.

Diagnostic Assessment

Blood pressure at this visit was 119/80 (95th percentile for age and height). Other vital signs were normal, and the patient was afebrile with a normal physical examination. An MRI of the abdomen with contrast was obtained and demonstrated a new 1.5 cm nodular structure between the superior pole of the right kidney and the inferior vena cava concerning for metastatic pheochromocytoma. MRI also revealed an enlarging retrocrural lymph node. The patient then underwent Positron emission tomography-DOTA-$(Tyr)^3$-octreotate (PET-DOTATATE) imaging, which showed foci of increased DOTATATE uptake at the left diaphragmatic crus and right retrocrural lymph node, suspicious for recurrent or metastatic disease (Fig. 2). Laboratory tests revealed elevated normetanephrine at 885 pg/mL (4832 pmol/L) (normal reference range <148 pg/mL; <808 pmol/L).

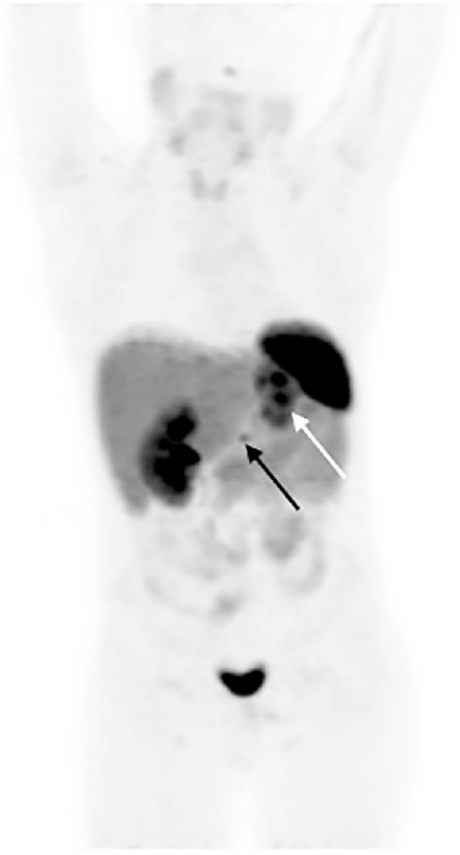

Figure 2. Positron emission tomography-DOTA-$(Tyr)^3$-octreotate reveals foci of increased DOTA-$(Tyr)^3$-octreotate uptake at the left diaphragmatic crus (white arrow) and right retrocrural lymph node (black arrow).

Treatment

Following the visit in the oncology clinic, the patient was evaluated by the nephrology service for hypertension in the setting of suspected pheochromocytoma with a plan for alpha blockade with phenoxybenzamine followed by beta blockade with

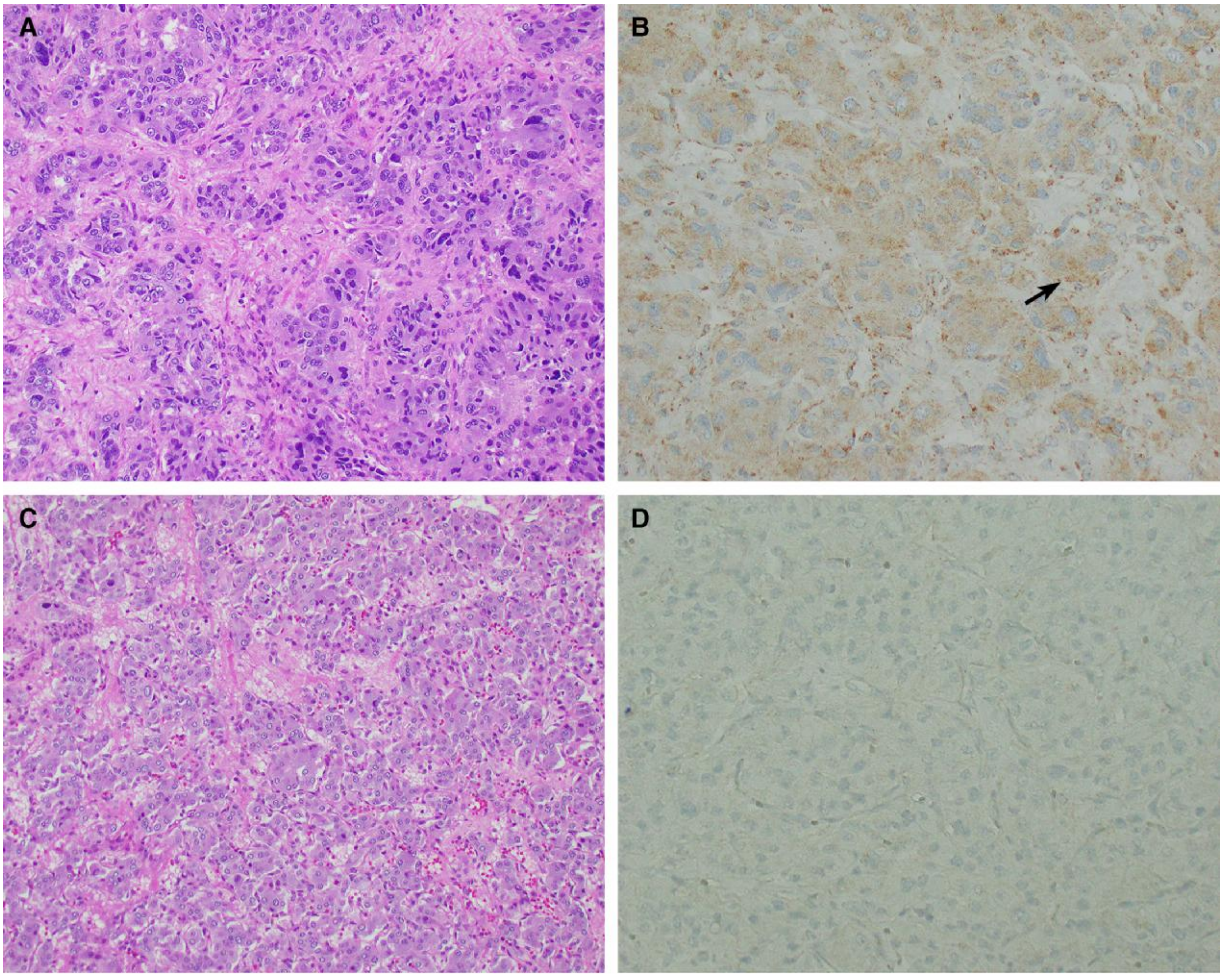

Figure 3. Pathologic change of the tumors. (A and B) Original right adrenal pheochromocytoma with H&E stain (A, 10×) showing nests of tumor cells with variable pleomorphism, forming Zellballen architecture. SDHB immunohistochemistry of the original right adrenal pheochromocytoma (B, 20×) demonstrating diffuse positivity (brown color, as indicated by an arrow) in the tumor cell cytoplasm. (C and D) Retrocaval mass/paraganglioma with H&E stain (C, 10×) showing nests of tumor cells and immunohistochemistry of SDHB (D, 20×) demonstrating negative reactivity.

Abbreviations: H&E, hematoxylin and eosin.

propranolol in preparation for surgery. The child underwent exploratory laparotomy with excision of a 2 cm retrocaval mass and 2 cm interortocaval mass. During the procedure, he also underwent retroperitoneal lymphadenectomy and completion of a right adrenalectomy.

The tumors were sent for pathology following excision. The retrocaval mass demonstrated a small fragment of uninvolved adrenal gland adjacent to a pheochromocytoma vs paraganglioma with loss of SDHB expression. Histological and immunophenotypical features favored a recurrent pheochromocytoma from the residual right adrenal gland or a new paraganglioma from around the residual right adrenal gland. The infrarenal intraaortic caval and interaortic caval tumor specimens also showed nodules of paraganglioma with a variably thick capsule adjacent to the lymph node. The tumor (Fig. 3C) showed the same pathologic changes as the original right adrenal tumor (Fig. 3A), both composed of nests of large cells with a surrounding fibrovascular septa, round to oval with variable pleomorphism, forming Zellballen architecture and surrounded by sustentacular cells. The tumor cells showed decreased SDHB staining (Fig. 3D) compared with prior right adrenal gland (Fig. 3B) and left adrenal gland pheochromocytoma (data not shown). There was no definitive evidence of metastatic disease. Overall, primary paragangliomas were favored as a diagnosis, although it was not possible to completely differentiate metastasis from multiple primary paragangliomas arising from adjacent sympathetic and parasympathetic ganglia. Retroperitoneal lymph nodes were also negative for malignancy.

Because the tumors were more consistent with primary paragangliomas rather than metastatic disease, no additional adjuvant therapy was pursued following surgical management and resection.

Outcome and Follow-up

Since resection of the paragangliomas, the patient has been followed regularly in the oncology clinic every 4 months with screening MRIs with intravenous contrast and PFM at these visits. PFM have normalized during follow-up visits. Six months after resection of his primary paragangliomas, his MRI demonstrated new mesenteric lymphadenopathy. However, PET-DOTATATE reassuringly did not show avidity of these lymph nodes, suggesting venous congestion as the cause of the lymphadenopathy. He is now 1 year out from his last paraganglioma resection with no concerns for recurrent

or metastatic disease. He continues on hydrocortisone for adrenal insufficiency.

Discussion

Here we present a diagnostically challenging case, wherein initial clinical suspicion was highest for recurrent or metastatic pheochromocytoma but pathology of the resected tumors favored the diagnosis of multiple primary paragangliomas. This patient has had 3 lifetime occurrences of PPGLs, with multiple paragangliomas noted during the third presentation, despite bilateral adrenalectomy. Cases of multiple paragangliomas occurring synchronously are rare but have been reported in the literature (10-12). Studies have implicated PVs in *SDHD* and *SDHB* in the development of multiple paragangliomas, though patients with hereditary pheochromocytoma/paraganglioma syndrome due to a *SDHB* PV are at much higher risk of presenting with metastatic PPGL, rather than multiple primaries (5, 10, 11). Children with VHL typically present with norepinephrine-secreting pheochromocytomas, and the risk for metastatic disease is reported at 5% to 8% (5). VHL is also known to be associated with a greater likelihood of having a second lifetime PPGL after initial diagnosis (6).

In general, between 10% and 15% of pheochromocytomas and up to 50% of abdominal paragangliomas are metastatic (1, 2). Metastatic disease can be diagnosed based on the presence of tumors in parts of the body that typically do not display chromaffin cells. Specific pathologic features of PPGLs tend to be overrepresented in metastatic cases. Tumors that display invasive behavior consisting of vascular or capsular invasion as well as fat extension are associated with metastasis (2, 13). Other concerning pathologic features include irregular cell nests and cytologic features like spindle cells, high mitotic counts, and aggravated pleomorphism (2, 13). Positive neuroendocrine markers on pathology with negative keratin stains also favor metastatic PPGL over a primary tumor (2). Several histopathological scoring systems have been developed to help stratify risk for recurrent or metastatic disease based on these features including the Pheochromocytoma of the Adrenal Gland Scaled Score and Grading System for Adrenal Pheochromocytoma and Paraganglioma (13). The Pheochromocytoma of the Adrenal Gland Scaled Score was the first scoring system developed but has fallen out of favor due to variable intra- and interrater reliability. The Grading System for Adrenal Pheochromocytoma and Paraganglioma combines histopathology and clinical data, and higher scores have been shown to be associated with increased risk of recurrence and distant metastatic disease (13). These score systems are not formally validated in pediatric patient tumors.

This case was diagnostically challenging due to discordance between imaging and pathology results. Imaging was more concerning for metastatic disease based on the location of the tumor and the presence of an avid of a retrocrural lymph node on PET-DOTATATE. While imaging studies are helpful in localizing tumors and evaluating for metastasis, it is important to remember that pathology is the gold standard for diagnostic confirmation of PPGLs. Systemic therapy should not be initiated until after pathology evaluation.

Resolving the diagnostic dilemma in this case was critically important for this patient's long-term care, given the differences in management approaches for metastatic and multiple primary PPGLs. For nonmetastatic disease, complete surgical resection is curative (1-3). Alpha receptor blockade first followed by beta blockade prior to surgical intervention is critical to avoid hypertensive crisis. For metastatic or malignant disease, additional treatment modalities may be utilized, including radionuclide treatment or chemotherapy (1-3). Other treatment options in metastatic PPGL include tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and immune checkpoint inhibitors (2, 3). Due to high rates of recurrence and risk of latent metastatic disease, all patients diagnosed with PPGLs require lifelong surveillance imaging (13).

Learning Points

- Genetic testing should be considered for all patients (especially in the pediatric population) presenting with a PPGL given high associations with germline mutations and cancer predisposition syndromes.
- While imaging and laboratory findings can aid in diagnosis of PPGLs, excisional biopsy is the gold standard for diagnostic confirmation.
- For nonmetastatic PPGLs, surgical resection alone is curative.
- PPGLs have high rates of recurrence, and patients require lifelong surveillance. Rates of recurrence are increased for patients with PVs in *SDHx* genes and *VHL*.

Contributors

All authors made individual contributions to authorship. J.M. was involved in the diagnosis and management of the patient and obtained informed consent for the case report. J. M. reviewed and edited the manuscript. K.M. prepared the primary text and performed a review of the literature. Q.W. was the pathologist for the patient and prepared histology images. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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