

Retroperitoneal Peripheral Hemangioblastoma: A Case Report and Review of the Literature

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Central nervous system hemangioblastomas are uncommon tumors of controversial etiology that are usually found in the posterior fossa of the cranial cavity, retina, and spinal cord. Peripheral involvement is rare; only isolated case reports have been identified. We report an unusual case of hemangioblastoma involving the retroperitoneum. A 47-year-old African-American man presented with polycythemia on routine laboratory testing. Computed tomography revealed a large retroperitoneal mass near the pancreas, in a left suprarenal location, without adrenal involvement and without attachment to a nerve. Although hemangioblastoma may be associated with the von Hippel-Lindau syndrome, this patient did not have any of the stigmata of this disease. The histologic features included a highly vascular tumor with cellular areas composed of plump, pleomorphic spindle and epithelioid (stromal) cells with variable cytoplasmic lipid vacuoles and hypocellular areas with inflammatory cells and collagenous fibrils. Immunohistochemical staining showed that the tumor (stromal) cells were positive for vimentin, calponin, S-100 protein, neuron-specific enolase, and CD57 and negative for glial fibrillary acidic protein, cytokeratins, epithelial membrane antigen, CD34, HMB-45, desmin, and the actins. These morphologic and immunohistochemical findings are consistent with hemangioblastoma. To our knowledge this is the first reported case of a hemangioblastoma in this location. Based on this case we conclude that hemangioblastoma may occur in the retroperitoneum and outside of the central nervous system in a patient without von Hippel-Lindau syndrome. The immunoprofile of this case suggests that hemangioblastomas are mesenchymal neoplasms exhibiting both neural and myofibroblastic differentiation.

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PERIPHERALLY located hemangioblastomas are rare. There have been no previous reports of a peripheral hemangioblastoma in the retroperitoneum. We present a patient with a retroperitoneal peripheral hemangioblastoma, without von Hippel-Lindau syn-

drome or obvious peripheral nerve involvement, and discuss the morphologic and immunohistochemical findings and differential diagnosis.

Case Report

A 47-year-old African-American man was found to have polycythemia with an erythrocyte count of 6.15 million/dL, a hemoglobin of 19.1 g/dL, and a hematocrit of 57.2%. A number of roentgenographic examinations were performed. Computed tomography of the abdomen before and after intravenous contrast demonstrated a left-sided 6.7 cm retroperitoneal mass, contiguous with the upper pole of the kidney, near the left adrenal gland, and associated with the tail of the pancreas. There was inhomogeneous contrast enhancement. Magnetic resonance imaging using intravenous gadolinium demonstrated a solid and cystic 7.0-cm soft tissue mass of the left retroperitoneal region that diffusely enhanced and demonstrated considerable cystic change in the central portion (Fig 1). A normal left adrenal gland was not visualized. No lymph node enlargement was noted.

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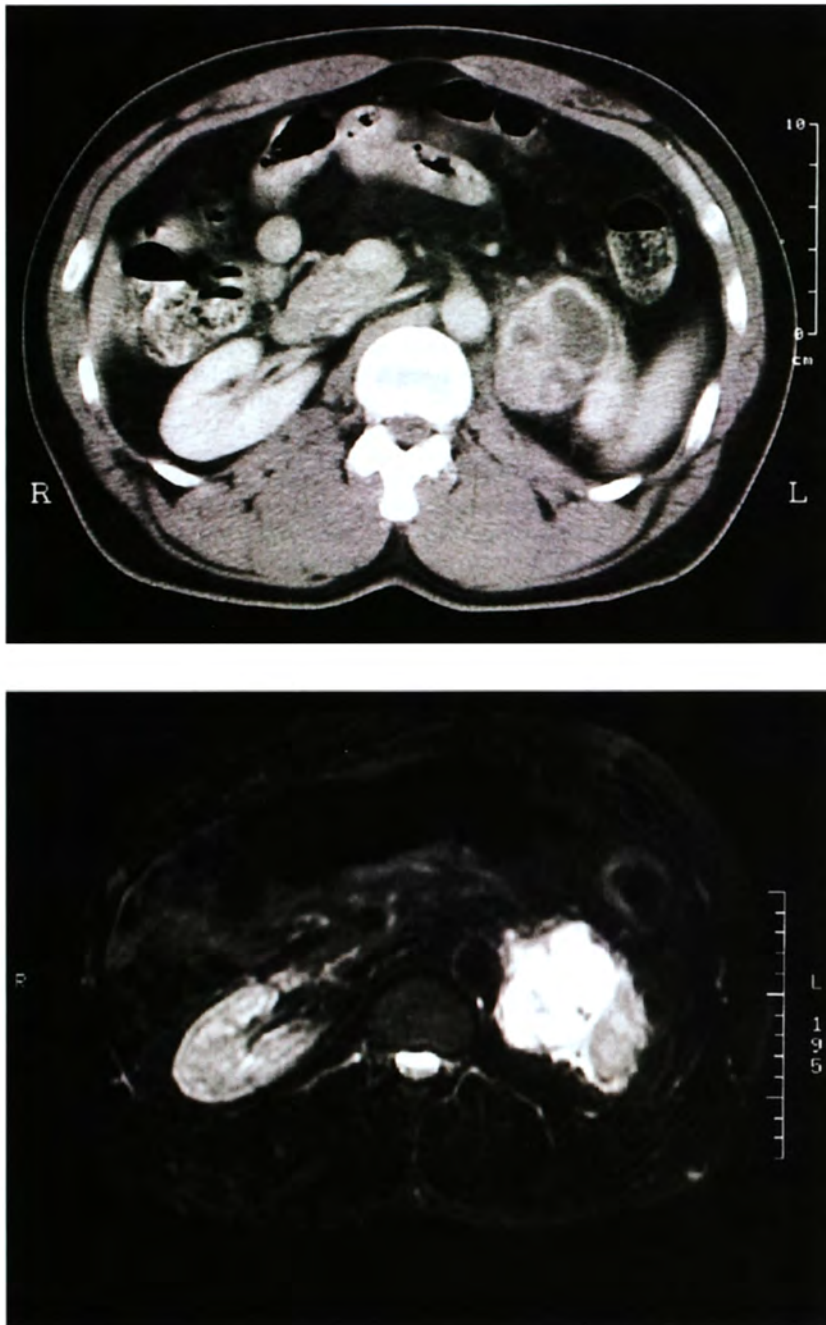


Figure 1. Computed tomography scans without (top) and with (bottom) contrast enhancement demonstrating cystic and solid components of this large, highly vascular retroperitoneal tumor.

The patient's past medical history was negative for hypertension, diabetes, or other pancreas, heart, liver, lung, adrenal, middle ear, eye, epididymis, or kidney diseases. The patient does have a history of colitis, but annual colonoscopy has been unremarkable. His family history was significant for three relatives with colon cancer. None of the stigmata of von Hippel-Lindau syndrome have been demonstrated in the patient or any of his family members. He does not smoke

tobacco or drink alcohol. He was not on any medications and has no known allergies.

Based on the radiographic study results, an exploratory laparotomy was performed with a left adrenalectomy and excision of the adjacent left retroperitoneal mass. Due to the large size of the lesion, the pleural space was entered at the same time as the retroperitoneal space, requiring the placement of a left chest tube. The spleen was uninvolved. While

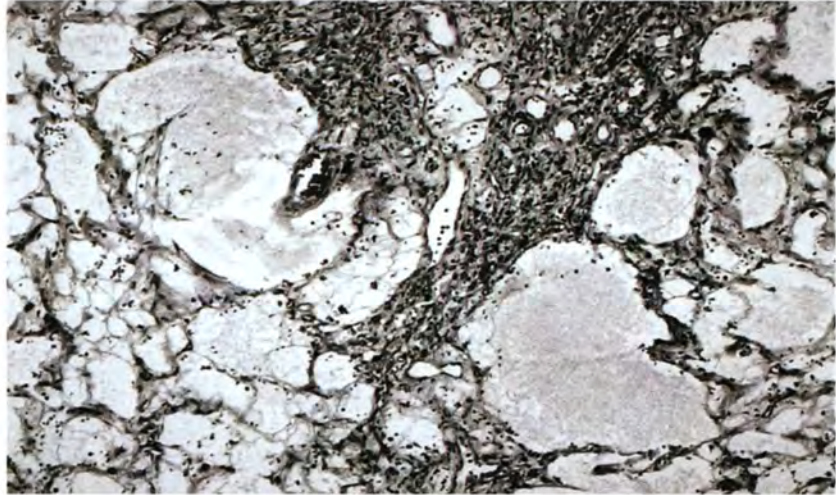


Figure 2. Low-magnification view of retroperitoneal peripheral hemangioblastoma showing cystic and solid areas.

there was macroscopic attachment to the superior pole of the adrenal gland and the pancreas, microscopic examination failed to identify tumor involvement of either of these organs.

After a diagnosis of a primary retroperitoneal hemangioblastoma was rendered, a thorough diagnostic evaluation to rule out von Hippel-Lindau disease was conducted. The patient did not have any integumentary abnormalities or skin discoloration. Postoperative radiographic assessment of the brain and abdomen failed to reveal any lesions of the brain and cerebellum and did not disclose any cysts or masses of the pancreas, kidneys, and liver. Visual acuity was slightly decreased, but correctable. Fundoscopic examination was normal, without evidence of retinal lesions. The results of the auditory examination were normal; the patient's hearing acuity was also normal. He did not have any middle or inner ear disturbances. Therefore, based on these findings we concluded that there was no evidence of associated von Hippel-Lindau syndrome. In summary, the patient's retroperitoneal mass was a solitary lesion.

The patient encountered no surgical complications and convalesced quickly after surgery. He is presently without any residual effects of the surgery and is being managed symptomatically for the polycythemia, which has not yet resolved following removal of the tumor.

Results

Grossly, the tumor was described as firm yellow, cystic, and hemorrhagic. Microscopically, the tumor had the classic features of a hemangioblastoma. At low power, there were alternating cellular and hypocellular areas with cystic change (Fig 2). The cellular areas were composed of spindled to plump stromal, or interstitial, cells that were arranged in a loose storiform growth pattern and admixed with epithelioid, lipid-filled multivacuolated cells (Fig 3). The cells demonstrated nuclear pleomorphism with smudgy chromatin but without

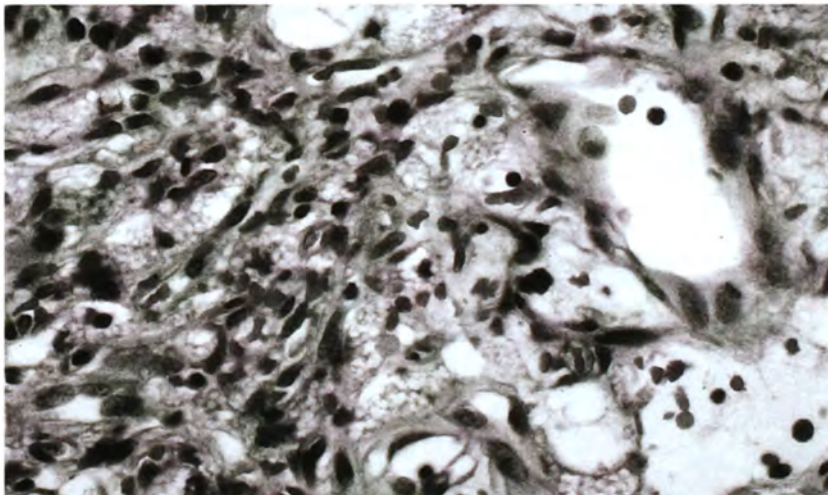


Figure 3. Higher-magnification view of retroperitoneal peripheral hemangioblastoma demonstrating the lipid-filled stromal cells of this capillary-rich tumor.

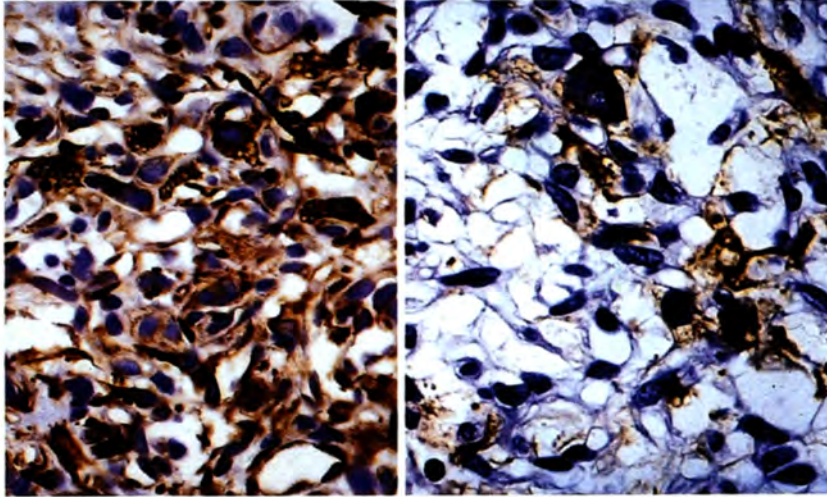


Figure 4. Vimentin (left) and calponin (right) staining in this retroperitoneal hemangioblastoma support a myofibroblastic mesenchymal phenotype.

increased mitotic activity. The hypocellular areas contained collagenous fibrils and extravasation of erythrocytes and chronic inflammatory cells, including lymphocytes, mast cells, and plasma cells. Variably sized vessels from small capillaries to medium-sized vessels were present throughout the tumor. Extramedullary hematopoiesis was not observed within the lesion.

Immunohistochemical stains revealed that the stromal tumor cells were positive for vimentin (Fig 4), calponin (a marker for myofibroblastic or smooth muscle phenotype; Fig 4), S-100 protein (Fig 5), neuron-specific enolase (NSE; Fig 5), and Leu7 (CD57), and were negative for glial fibrillary acidic protein (GFAP), desmin, actins, HMB-45, CD34, epithelial membrane antigen, and cytokeratins.

Discussion

Peripheral hemangioblastomas are rare. There have been no previous reports of a retroperitoneal hemangioblastoma. Previously reported cases of peripheral hemangioblastomas include those in the liver,^{1,2} lungs (same patient as the liver hemangioblastomas¹),² pancreas,³ kidney,^{4,6} urinary bladder,⁷ radial nerve,⁸ and sciatic nerve.⁹ Hemangioblastomas arising in the spinal nerve roots (multiple¹⁰ and C4 only⁹) and cauda equina^{9,11,12} also should be considered and included in this “peripheral” group. With the exception of the visceral (intraorgan) cases, all these have been identified as involving a specific peripheral nerve.⁹ Furthermore, all the previous cases of peripheral hemangioblastoma, with the excep-

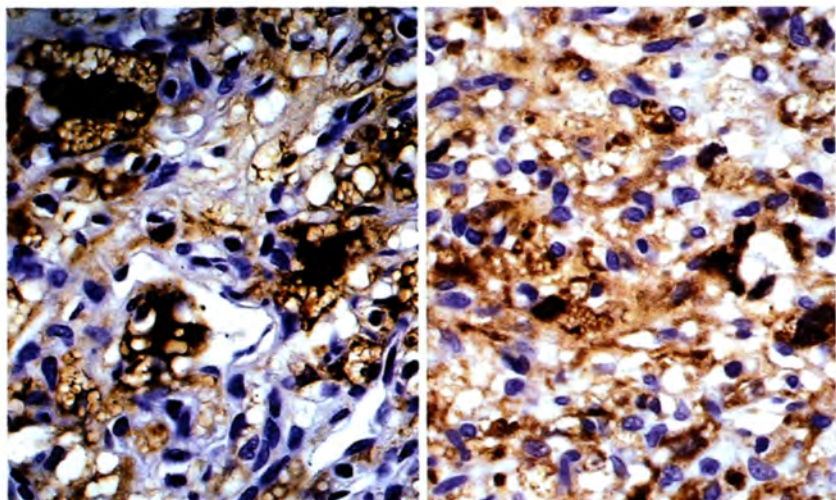


Figure 5. S-100 protein (left) and NSE (right) staining in this retroperitoneal hemangioblastoma support a neural phenotype.

tion of the radial nerve case that was not entirely worked up for von Hippel-Lindau syndrome,⁸ arose in the setting of one or more stigmata (including spinal or cauda equina hemangioblastoma) of von Hippel-Lindau syndrome. Our case is different because it does not appear to involve a known peripheral nerve, it is not involving a visceral organ, and it is not in the setting of von Hippel-Lindau syndrome.

The exact percentage of patients with hemangioblastoma with von Hippel-Lindau syndrome is unknown. However, recent studies suggest that the VHL gene, mapped to chromosome 3p25, is a tumor suppressor gene^{13,14} and plays a role in development of hemangioblastoma, even in patients who do not have von Hippel-Lindau syndrome.¹⁵ Thus, it is possible that this gene may play a role in all hemangioblastomas. It would be helpful to study this possibility further with the current case since it is a solitary, nonvisceral, and peripheral hemangioblastoma.

The radiographic findings of the current case is consistent with radiographic findings of classic cerebellar hemangioblastoma.¹⁶ Our tumor was associated with a large cystic component. It was a discrete mass and, because it was contrast enhancing, showed evidence of increased vascularity.

Peripheral hemangioblastomas, including our case, are histopathologically identical to their central nervous system counterparts. These lesions are composed of varying proportions of endothelial-lined capillaries, larger blood vessels, cystic spaces, and interstitial or stromal cells. The stromal cells are rounded, spindle, or polygonal and often contain variable amounts of neutral lipid material. Their nuclei are generally uniform; however, they may be quite pleomorphic and hyperchromatic, as in the current case. Lesions in which the stromal cells predominate have been termed the *cellular variant*; tumors with a predominant vascular component are known as the *reticular variant*.^{16,17} Mast cells are commonly identified in hemangioblastomas.¹⁸ Foci of extramedullary erythropoiesis are occasionally encountered and result from the tumoral production of erythropoietin.¹⁹ Mitotic figures are absent or rare and are of no prognostic significance.

Immunohistochemically, the vascular and stromal cell components of hemangioblastomas exhibit differing antigenic profiles. Markers for endothelial cells, including factor VIII-related antigen²⁰⁻²⁶ and *Ulex europaeus* agglutinin lectin,^{21,22,24} are generally restricted to the endothelial cells and absent in stromal cells. In contrast, most stromal cells express vimentin²¹ and NSE.^{22,27,28} Occasional stromal cells also stain with antibodies to

S-100 protein²¹⁻²⁴ and GFAP.^{15,20-26} Most investigators interpret these cells as entrapped astrocytic elements or as evidence of GFAP uptake by stromal cells rather than that they indicate astrocytic differentiation.¹⁷ The finding of hemangioblastomas outside of the central nervous system also argues against an astrocytic derivation for these tumors.⁸ Interestingly, our case was negative for GFAP, as might be expected outside of the central nervous system in nonneural tumors. However, this tumor was positive for S-100 protein, as well as NSE and Leu-7 (CD57), supporting a neural phenotype for this tumor. The S-100 positivity is also interesting because this tumor was not associated with a known nerve like many of the other peripheral nonvisceral hemangioblastomas. The only visceral tumor previously studied with immunohistochemistry, a hepatic tumor,¹ was negative for S-100 protein. On the other hand, nerve-associated tumors, such as schwannomas, are known to occur in the retroperitoneum without a specific known nerve involvement. It is possible that this case did involve a nerve that was not detected clinically, radiographically, or pathologically.

Hemangioblastomas also stain with antibodies to erythropoietin,^{24,29} renin,²⁴ and progesterone receptors.³⁰ It is well understood that the erythropoietin in this tumor causes polycythemia and extramedullary hematopoiesis.¹⁹ Polycythemia occurs in 10% to 20% of patients with hemangioblastoma.^{16,31} Our patient has polycythemia that did not resolve with complete removal of the hemangioblastoma. However, it is possible that this patient either has an unrelated idiopathic polycythemia or may have residual or additional undetected hemangioblastoma. The patient had no signs of hyperreninemia (ie, hypertension) or hyperprogesteronemia, although this was not specifically evaluated in this patient.

Factor XIIIa³² has been identified in some hemangioblastomas and is thought to be related to "fibrohistiocytic" neoplasms, which are typically composed of myofibroblasts. Other researchers have proposed a smooth muscle phenotype for hemangioblastomas based on muscle-specific actin and desmin immunoreactivity.^{21,24} The current tumor was negative for desmin and the actins. Factor XIIIa is known to be a marker for nonneoplastic "passenger histiocytes" in fibrohistiocytic neoplasms, which are otherwise thought to be composed of myofibroblasts. The positivity of calponin³³ and negativity for the actins and desmin in the current tumor support the possibility of a myofibroblastic or possibly myopericytic phenotype.²⁵ This marker has not been previously studied in these tumors and is strong pheno-

typic evidence favoring at least partial myofibroblastic differentiation in these lesions.

Markers of epithelial (cytokeratin and epithelial membrane antigen^{21,24}), neuroendocrine (chromogranin and synaptophysin^{21,22}), and neuroectodermal (chromogranin, synaptophysin, neurofilament protein^{21,22}) differentiation are generally negative in these neoplasms, assisting in their differential diagnosis from other lesions and determining hemangioblastoma to be unrelated to neuroendocrine, neuroectodermal, or epithelial phenotypes.

The morphologic differential diagnosis of hemangioblastoma in a retroperitoneal (nonvisceral) location includes metastatic renal cell carcinoma, extraorbital giant cell angiofibroma,³⁴ hemangiopericytoma, angiomylipoma, and cellular hemangioma. The immunophenotypic differential includes retroperitoneal neural and myofibroblastic lesions.

Numerous studies have evaluated the distinction between renal cell carcinoma and hemangioblastoma,^{24,30,35,36} particularly since both lesions may occur in the setting of von Hippel-Lindau syndrome. Morphologically, our tumor is distinctive due to the number of typical lipid-filled stromal cells. In general, epithelial membrane antigen is positive in renal cell carcinoma but is negative in hemangioblastoma. Furthermore, S-100 protein, NSE, CD57, and calponin immunostains are typically negative in renal cell carcinoma.

A number of pathologists would not separate extraorbital giant cell angiofibroma³⁴ from pleomorphic variants of hemangiopericytoma or solitary fibrous tumor. Although the current lesion demonstrated some of the pleomorphism described in giant cell angiofibroma,³⁷ giant cell angiofibroma lacks the lipid-filled stromal cells of hemangioblastoma. Furthermore, all the above lesions are CD34 positive, which was negative in the stromal cells of our hemangioblastoma. Finally, hemangiopericytoma, too, lacks the lipid-filled stromal cells of hemangioblastoma.

Angiomylipoma has a blend of vessels, immature smooth muscle cells, and fat and lacks the lipid-filled stromal cells of hemangioblastoma; hemangioblastoma lacks the smooth muscle features and abundant fat of angiomylipoma.

Although once thought to be a tumor of vascular origin, hemangioblastoma is too complex for a cellular hemangioma, lacks vascular markers, and has lipid in its stromal cells.

Despite the foam cells and similar S-100 positivity of retroperitoneal schwannoma, its morphology is markedly different than that of hemangioblastoma. Retroperitoneal schwannomas are often GFAP and sometimes

cytokeratins (cross-reactivity with GFAP) positive,³⁸ both of which were negative in our tumor.

It is generally unusual for benign myofibroblastic lesions from the fibroblastic and fibrohistiocytic categories of soft tissue tumors to occur in a retroperitoneal location and they would not be considered in the morphologic differential diagnosis of this lesion. Inflammatory myofibroblastic tumor may occur in the retroperitoneum, but lacks the vasculature and lipid-filled cells of hemangioblastoma.

In summary, this is the first reported case of a retroperitoneal hemangioblastoma. It is not associated with the visceral, the central nervous system, or von Hippel-Lindau syndrome. This benign mesenchymal neoplasm has features of both neural and myofibroblastic differentiation. It can be distinguished from lesions in its differential diagnosis by its morphology and immunohistochemical features.

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