Fibrous meningioma in a patient with von Hippel–Lindau disease: a genetic analysis

Case report

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Meningioma has been included in the constellation of tumors associated with von Hippel–Lindau (VHL) disease in previously published reports. It is unclear whether these tumors are an uncommon component of VHL disease or are more readily detected in these patients because of the frequency with which they undergo central nervous system imaging as part of the routine management of VHL disease. The authors report the case of a patient with VHL disease in whom a progressively enlarging supratentorial mass developed and was diagnosed as a hemangioblastoma because of its appearance on serial magnetic resonance images. At surgery the tumor displayed the typical features of a meningioma and was given the histological diagnosis of fibrous meningioma. Single-stranded conformational polymorphism analysis of the tumor DNA revealed a loss of heterozygosity at the neurofibromatosis Type 2 gene locus, known to be associated with sporadically occurring meningiomas. Despite this finding, the VHL gene locus on the allele from the patient’s unaffected parent was normal. Thus it is unlikely that the occurrence of this patient’s fibrous meningioma was associated with underlying VHL disease. Given the high frequency of neuroimaging sessions in patients with VHL disease, some supratentorial lesions that have been given radiological diagnoses of hemangioblastomas may be incidental meningiomas.

KEY WORDS • von Hippel–Lindau disease • meningioma • loss of heterozygosity

Patients with the tumor suppressor syndrome VHL disease are predisposed to the development of a variety of different tumors, most notably, cerebellar, medullary, and spinal hemangioblastomas; retinal angiomatos; and renal cell carcinomas (Table 1). Although meningiomas do not occur frequently in patients with VHL disease, several reports, including the classic review of this disease by Melmon and Rosen, have included meningioma as a rare manifestation of VHL disease.

Because most sporadically occurring meningiomas exhibit LOH at the NF2 gene locus, we assayed for LOH at both VHL and NF2 gene loci in our patient’s tumor to clarify whether this patient’s meningioma was associated with his VHL disease or was an incidental occurrence.

Case Report

History. This 37-year-old man with well-documented VHL disease had undergone three resections for central nervous system hemangioblastomas (one cerebellar, one spinal, and one medullary) as well as bilateral partial nephrectomies for renal cell carcinoma. A routine follow-up MR image demonstrated a new 1.2-cm superficial, uniformly enhancing mass in the right frontal convexity that was interpreted to be a supratentorial hemangioblastoma (Fig. 2). Given the patient’s diagnosis of VHL disease, the typical MR imaging appearance of a hemangioblastoma, and the fact that the man had never undergone radiation therapy, this mass was thought to be a hemangioblas-
toma of the cerebrum, a rare but generally acknowledged manifestation of the disease. Because the tumor was small and asymptomatic, it required no therapy.

Examination. Two years later, the patient returned to our VHL disease clinic complaining of right frontal headaches. An MR image revealed that the tumor had grown to a volume of $2 \times 2 \times 2.5$ cm (Fig. 2 right). Surgical removal of the enlarging, symptomatic tumor was deemed to be indicated.

Operation. At surgery following opening of the dura mater, we identified a soft, rubbery, relatively avascular tumor that was imbedded in the surface of the right frontal lobe approximately 3 cm from the midline. The tumor was entirely extraaxial and did not breach the pia or the arachnoid. The tumor was removed en bloc with a piece of surrounding dura mater measuring approximately 3 cm in diameter, and was sent for pathological analysis. The intraoperative diagnosis was meningioma.

Pathological Examination. Hematoxylin and eosin staining revealed irregular bundles of elongated cells with spindle-shaped nuclei and occasional intranuclear pseudoinclusions (Fig. 3). This finding contrasted sharply with the typical hemangioblastoma appearance, which is characterized by proliferation of stromal cells with foamy cytoplasm and extensive vascularization. A pathological diagnosis of fibrous meningioma was made.

Genetic Analysis. Microdissection of neoplastic cells from the tumor tissue was performed using a previously described technique. After DNA extraction and amplification of the polymorphic VHL gene promoter region achieved using markers 104 and 105, SSCP analysis was performed. Two VHL alleles could be separated after analysis of the meningioma sample. Hemangioblastoma samples, which previously had been removed from the same patient (used here as a positive control), however, revealed evidence of only one VHL allele. Nevertheless, genetic analysis of the meningioma revealed LOH only at the NF2 gene locus (Fig. 4).

Discussion

von Hippel–Lindau disease is an autosomal-dominant, tumor-predisposing syndrome with an estimated incidence of one in 36,000 live births and nearly complete penetrance. Characteristic manifestations include cerebellar, medullary, and spinal hemangioblastomas; retinal angiomas; endolymphatic sac tumors; renal cell carcinomas; pancreatic cysts & tumors; pheochromocytomas; and epididymal cystadenomas. The VHL gene is a tumor suppressor gene that follows Knudson’s two-hit model and has been identified at chromosome 3p25–26.

The VHL gene product, pVHL, is a multifunctional tumor suppressor protein that localizes either to the nucleus or cytoplasm in a cell density–dependent manner. One of the key functions of pVHL is to bind to and target HIF-1 for ubiquitin-mediated degradation by protease under normoxic conditions. Hypoxia-inducible factor 1 is the coordinator of the cell’s response to hypoxia. Through transcriptional regulation, HIF-1 enhances glucose metabolism and the expression of VEGF. Therefore, without pVHL, HIF-1 constitutively augments energy metabolism.

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**TABLE 1**

*Common manifestations of von Hippel–Lindau disease*

<table>
<thead>
<tr>
<th>Common manifestation</th>
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<tr>
<td>cerebellar, medullary, &amp; spinal hemangioblastomas</td>
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<tr>
<td>retinal angiomas</td>
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<tr>
<td>endolymphatic sac tumors</td>
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<tr>
<td>renal cell carcinomas</td>
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<tr>
<td>pancreatic cysts &amp; tumors</td>
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<tr>
<td>pheochromocytomas</td>
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<td>epididymal cystadenomas</td>
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**Fig. 1.** Drawing demonstrating Knudson’s “two-hit” model of tumor suppressor genes. To develop a tumor, the tumor suppressor gene locus on both chromosomes must be nonfunctional. Acquisition of two nonfunctional copies of the gene can occur by inheriting one (dashed ×) and losing the other spontaneously (solid ×), as is the case in familial tumor syndromes such as VHL disease (upper), or by losing both copies spontaneously (lower).

**Fig. 2.** Gadolinium-enhanced axial T1-weighted MR images of the cerebrum revealing a superficial, uniformly enhancing mass in the right frontal convexity. Initially the greatest diameter of the lesion measured 1.2 cm (left); 2 years later the lesion measured $2 \times 2 \times 2.5$ cm (right).
and stimulates angiogenesis. In addition, the absence of pVHL itself has been shown to increase VEGF expression through release of both transcriptional and posttranslational regulation. These mechanisms could explain the highly vascular nature of tumors associated with VHL disease, especially hemangioblastomas, all of which do not express functional pVHL. Besides enhanced angiogenesis, losses of the ability to leave the cell cycle (that is, enter G0) and properly assemble a fibronectin extracellular matrix are also tumorigenic events. Functional pVHL is required for the retention of both of these normal activities (Fig. 5).

Meningiomas are tumors composed of meningothelial cells and have an annual incidence of approximately six per 100,000 people. Fibrous meningiomas are a common subtype and are characterized histopathologically by wide fascicles of spindle-shaped tumor cells that usually do not have whorls or psammoma bodies. Most sporadically occurring meningiomas demonstrate LOH of the NF2 tumor suppressor gene.

Numerous authors have previously reported that meningiomas are part of the constellation of tumors associated with VHL disease. The characteristics of the case presented here, however, contradict that assertion. The lack of LOH at the VHL gene locus and the presence of LOH at the NF2 gene locus in this patient’s fibrous meningioma, coupled with the presence of LOH at the VHL gene locus in a cerebellar hemangioblastoma removed from the same patient, suggests that the meningioma was probably incidental and not associated with VHL disease.

An argument can be made that failure to detect LOH at the VHL gene locus does not necessarily ensure expression of pVHL. It is possible that the VHL gene can be inactivated by other mechanisms that would not be detected by LOH analysis, such as microdeletion, point mutation, hypermethylation, or a method not yet discovered. In our experience, however, the loss of the wild-type VHL allele (second hit) in tumors clinically known to be associated with VHL disease is almost always due to a large deletion that can be detected by LOH.

Supratentorial lesions that develop in patients with VHL...
disease and exhibit an MR imaging appearance similar to that shown in our patient are generally considered to be hemangioblastomas. Nevertheless, rarely has this diagnosis been confirmed histologically. Thus, many of these tumors may actually be incidental meningiomas that are discovered because of the frequent imaging that occurs in patients with VHL disease.

It is noteworthy that, during an extensive literature search, we found three previous case reports of meningiomas that had developed in patients with VHL disease.\(^{2,27,35}\) One of these tumors was histologically characterized as consistent with the current meningioma classification schema defined by the World Health Organization.\(^{2,16}\) The other two meningiomas, however, were characterized as angio-blastic meningiomas; according to the current classification schema, these tumors would now be classified as mening-geal hemangioblastomas.\(^{3,27,35}\)

### Conclusions

Results in this case suggest that meningiomas may not be part of the spectrum of tumors associated with VHL disease. We propose that genetic analysis for LOH at the VHL gene locus be used not only to find potential VHL disease–associated neoplasms but also to rule them out.

### References

30. Rutledge MH, Xie YG, Han FY, et al: Deletions on chromo-

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**Fig. 5.** Diagram showing tumor suppressor functions of pVHL. Loss of functional pVHL leads to the manifestations of VHL dis-ease. **Pointed arrowheads** indicate activation; **flat arrowheads** indicate inhibition.
some 22 in sporadic meningioma. Genes Chromosomes Cancer 10:122–130, 1994

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