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Case Report

Hemangioblastoma of the optic nerve producing bilateral optic tract edema in a patient with von Hippel–Lindau disease

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Abstract

Background: The authors present a novel case of a hemangioblastoma of the optic nerve producing bilateral optic tract edema in a patient with von Hippel–Lindau disease (VHL). This is the only case in the literature documenting optic tract edema secondary to a hemangioblastoma of the optic nerve.

Case Description: The patient was a 34-year-old female in whom this lesion was causing retro-orbital pain and proptosis. She had previously lost vision in the symptomatic eye secondary to a retinal hemangioblastoma. The optic nerve lesion was excised by sectioning the optic nerve both proximally and distally to the lesion. There were no complications and patient's symptoms resolved postoperatively. A follow-up magnetic resonance imaging (MRI) scan revealed complete excision of the mass and resolution of the optic tract edema.

Conclusion: Optic nerve hemangioblastomas in patients with VHL are rare, but are manageable with meticulous microneurosurgery and with appropriate patient expectations. This is the first known case of an optic nerve hemangioblastoma producing bilateral optic tract edema, which resolved after resection of the prechiasmal tumor. Hemangioblastoma should remain in the differential diagnosis of optic nerve tumors, especially in the setting of VHL.

Key Words: Hemangioblastoma, optic nerve mass, optic-tract edema, von Hippel–Lindau

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INTRODUCTION

Von-Hippal–Lindau (VHL) disease is an autosomal dominant disorder originating from a mutation of the VHL tumor suppressor gene on chromosome 3p25.[1,20] The prevalence of VHL in the general population is nearly 1 in 36,000.[20] VHL disease is classically associated with renal cell carcinomas, renal cysts, pancreatic islet cell tumors, pheochromocytomas, and endolymphatic sac tumors.[1] Intracranial and retinal hemangioblastomas are the central nervous system manifestation of VHL.[1,20] Seventy-two percent of patients with VHL will have a cerebellar hemangioblastoma.[1] Five to thirty-one percent of all patients found to have a cerebellar hemangioblastoma have subsequently been diagnosed with VHL.[1] Forty percent of all patients with VHL will have a spinal cord

hemangioblastoma.[1] Most patients, nearly 80%, with spinal cord hemangioblastomas will subsequently be diagnosed with VHL.[1] Fifty percent of patients with VHL have retinal capillary hemangioblastomas.[20]

Hemangioblastomas make up nearly 2% of all intracranial tumors and 10% of posterior fossa tumors in adults.[6,25,28] Most hemangioblastomas present as posterior fossa masses.[11,25] Less than 5% of hemangioblastomas present in the supratentorial compartment. Hemangioblastomas have been seen in the pituitary stalk, optic nerves, and the ventricles.[1] Hemangioblastomas are vascular tumors that readily enhance with contrast in radiographic imaging tests. Histologically, hemangioblastomas are typically well-circumscribed, vascular masses, which generally appear grossly red in color. Microscopically, hemangioblastomas are characterized by vacuolated stromal cells and a rich capillary network. It has been reported that the stromal cells are the true tumor cell of a VHL-associated hemangioblastoma.[3] The stromal cells have a loss of heterozygosity of the VHL gene while the endothelial and reactive glial cells that make up the remainder of the hemangioblastoma do not contain this same genetic malformation.[3]

It is common to see the reactive Rosenthal fibers mentioned above in brain adjacent to the mass. It is important to differentiate a hemangioblastoma from the much more malignant renal cell carcinoma. They often are very similar histologically, however, renal cell carcinomas are positive for CAM 5.2, RCC antigen, CD10, and EMA antibodies while hemangioblastomas are not.

Herein we report a case of an optic nerve hemangioblastoma in a patient with known VHL, which produced bilateral optic tract edema suggesting the diagnosis of an optic nerve glioma, and review the current literature.

CASE REPORT

This patient is a 34-year-old right-handed female with a known history of VHL disease. She presented to the neurosurgical service at Houston Methodist Hospital with a chief complaint of right retro-orbital pain and proptosis. She had previously undergone removal of a right retinal hemangioblastoma and was blind in the right eye, but the progressive pain and proptosis led to the discovery of a progressively enlarging lesion of the right optic nerve. Past history was notable for VHL and gastroesophageal reflux disease. In addition to the retinal lesion, she has previously undergone suboccipital craniectomy for excision of a cerebellar hemangioblastoma as well as a left sided acoustic neuroma. She harbors intramedullary tumors at the craniocervical junction as well as in the cauda equina. Her family history is significant for a son who has VHL. She has no knowledge of other family members with VHL as she does not know her biological father. Neurological examination is significant for blindness of the right eye and numbness in the perineum.

Magnetic resonance imaging (MRI) scans of the brain with and without gadolinium revealed an avidly enhancing mass of the right optic nerve distal to the optic chiasm involving the cisternal, canalicular, and orbital components of the nerve measuring 1.2 cm in maximal diameter [Figure 1a]. The mass was noted to have doubled in size in comparison to imaging performed 5 years prior. In addition, increased FLAIR signal was noted in the optic tracts bilaterally, which was not observed in the prior study [Figure 1c], suggesting the diagnosis of an infiltrating optic nerve glioma.

She underwent elective craniotomy and excision of the mass, which was performed through a standard fronto-temporal craniotomy. The sphenoid wing was drilled flush with the orbital roof and the dura was opened in a curvilinear fashion based on the sphenoid wing. The proximal Sylvian fissure was dissected sharply and gentle frontal lobe retraction was applied. The tumor was noted to have a red-tan appearance and was noted to tent the dura propria of the optic canal upward. The dura propria was incised sharply, and the orbital roof was opened utilizing a high speed diamond burr and 1 and 2 mm Cloward punches. The distal optic nerve was identified and divided followed by section of the nerve 1-2 mm distal to the chiasm. The ophthalmic artery was then identified, coagulated and cut [Figure 2].

Neuropathological diagnosis confirmed hemangioblastoma with the tumor having marked vascularity with a vacuolated stroma [Figure 3].

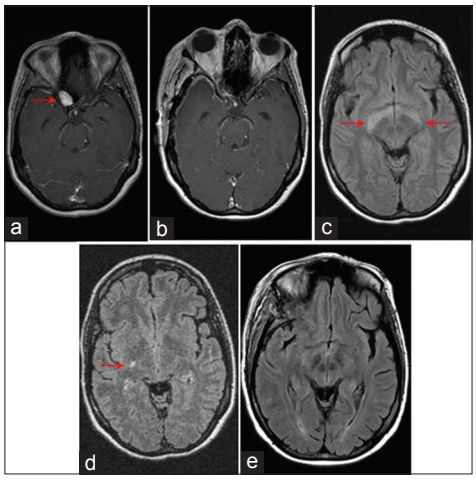

Figure 1: Comparison of preoperative and postoperative MRI scans. (a) Preoperative T1-weighted contrast enhanced axial MRI showing brightly enhancing right optic nerve lesion (Red arrow). (b) Postoperative T1-weighted contrast enhanced axial MRI showing gross total excision of tumor. (c) Preoperative FLAIR MRI shows hyperintensity of bilateral optic tracts (Red arrows). (d) FLAIR signal extends into the right lateral geniculate nucleus (Red arrow). (e) Postoperative FLAIR MRI shows the optic tract hyperintensity is resolved

The patient had an initial uncomplicated postoperative course and was discharged to home. She returned to the hospital 3 days after discharge with headaches. Repeat MRI of the brain revealed gross total excision of the mass as well as resolution of the FLAIR signal in the bilateral optic tracts. She is presently doing well, with resolution of her retro-orbital pain and no visual defect in the left eye.

DISCUSSION

VHL disease is an autosomal dominant syndrome that occurs secondary to defects in the VHL tumor suppressor gene. Patients with a complete deletion of the VHL gene have been found to have increased visual acuity and decreased incidence of retinal hemangioblastoma when compared with patients with a missense mutation.[10]

The development of tumors in VHL is thought to be a result of the "two-hit" hypothesis. One VHL allele is innately inactivated while the other allele is inactivated at the somatic level. This inactivation of the wild-type VHL allele is what leads to tumorogensis.[3]

The VHL protein functions by stimulating other angiogenic factors. The VHL protein is indirectly responsible for the ubiquitylation and thus deactivation of hypoxia-inducible factor (HIF).[3] In cells with defective VHL protein the HIF protein accumulates signaling hypoxia and leading to the upregualtion of other hypoxia-induced genes such as vascular endothelial growth factor (VEGF), erythropoietin, (EPO), platelet-derived growth factor, and transforming growth factor alpha.[3] As expected, all ocular hemangioblastomas express high levels of VEGF, HIF, and EPO.[3-5]

The differential diagnosis for a solitary optic nerve tumor includes optic nerve sheath meningiomas, gangliogliomas, meduloepitheliomas, hemangioblastomas, lymphoma, metastasis, granulomatous process, and retrobulbar neuritis.[21] In this case specifically, the radiographic findings and the history of VHL disease led to the presumption that this was a hemangioblastoma prior to surgical resection.

The imaging characteristics of an optic nerve hemangioblastoma help to differentiate it from other masses in the differential. Hemangioblastomas are generally well circumscribed, enhancing masses.[11] In this case, the right lateral geniculate nucleus has increased T2 and FLAIR signal [Figure 1d]. We postulate that the edema seen throughout the optic pathway is due to both inherent properties of the hemangioblastoma, as well as the presence of other secondary vasoactive properties or the secretion of other edema inducing substances. These tumors are highly vascular, and in a relatively confined area such as the optic nerve, the optic nerve sheath appears to serve as a barrier to the egress of tissue fluid from passive congestion in the microcirculation that leaks out into the extracellular space. This fluid in turn tracks backward along the fiber tracts of the optic nerve and tracts all the way back to the geniculate bodies and further. In addition, VEGF may play a role in the production of edema. It is well known that these tumors overexpress VEGF[22] Studies have demonstrated that anti-VEGF therapy can be effective in treatment of retinal hemangioblastomas. This includes the use

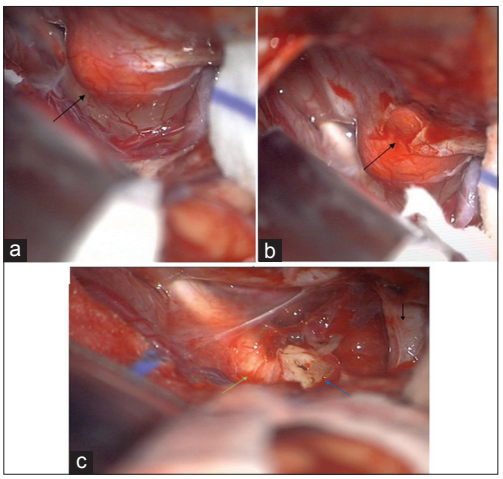

Figure 2: Right anterior skull base exposure (a) Right anterior skull base exposure showing reddish optic nerve tumor. (b) Dura propria incised over optic nerve tumor. (c) Optic nerve sectioned distal to the chiasm (Blue arrow). Black arrow denotes right internal carotid artery. Green arrow denotes the chiasm

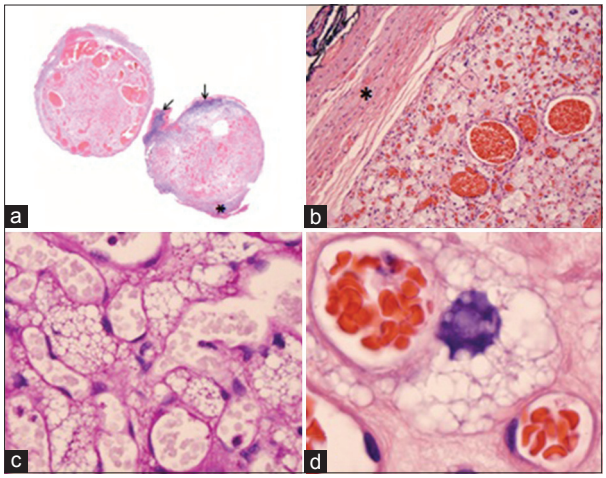

Figure 3: Histopathology of hemangioblastoma involving the optic nerve orbital and intracraneal portions. (a) Low power view of cross sections of central portion of the optic nerve with tumor. Notice the vascularized tumor in the center and residual optic nerve tissue (*). The edges show cautery artifact (arrows). H and E, ×1 original magnification. (b) Higher magnification showing residual nerve fibers (*). Notice the vascular nature of the tumor and the foamy cells of the stroma. H and E, ×10 original magnification. (c) PAS stain highlights the basement membrane of the vessels and absence of glycogen or mucin in the vacuoles of the stromal cells. Periodic Acid Schiff (PAS), ×20 original magnification. (d) Close up of the two components of the tumor, the vessels and the vacuolated stromal cells. H and E, ×100 original magnification

of Avastin[14] and other anti-VEGF treatment.[9] As evidenced in present case, the edema can track along the optic nerve and present as bilateral optic tract edema. This can lead to some doubt regarding the diagnosis, as an infiltrating optic pathway glioma would be more likely to produce this appearance. To our knowledge, this is the first reported case where bilateral optic tract and lateral geniculate ganglion edema is seen with an optic nerve hemangioblastoma. An angiogram is another imaging modality (not used in this case secondary to high clinical suspicion) that can be used to differentiate a hemangioblastoma from other known tumors of the optic nerve.[2] An angiogram showing a highly vascular mass would make the diagnosis of a hemangioblastoma far more likely than the other masses in the differential diagnosis.

In a thorough review of the English literature 19 cases, including the present case, of an optic nerve hemangioblastoma have been reported [Table 1]. Thirteen of the 19 cases (66%) were associated with VHL. The ages of the patients ranged from 15- to 64–year-old. There have been 12 females and 7 males diagnosed with this lesion. Eight of the patients had a purely intraoribital mass; 5 had a purely intracranial tumor; and 6 patients had a combination of an intracranial and intraorbital mass.

Meyerle *et al*. published a case series in 2008 reviewing the clinical course of retrobulbar hemangioblastomas.[20] In their series, they followed 300 patients with VHL, 9 of which developed retrobulbar hemangioblastomas. From this they concluded that the incidence of retrobulbar hemangioblastomas was 3% in a population with VHL disease. All nine patients had at least one other central nervous system (CNS) hemangioblastoma in addition to their retrobulbar tumor.

Without treatment all patients with an optic nerve hemangioblastoma will eventually lose vision in the affected eye. For this reason surgery is almost universally indicated. In Meyerle's series, all of the patients with a retrobulbar hemangioblastoma had a previously diagnosed retinal capillary hemangioblastoma presumably affecting their vision. The patient in this case also had a retinal lesion leaving her blind in her right eye. Obviously, when this is the case the surgeon can be more aggressive and full excision of the tumor via sectioning of the optic nerve itself can be performed.

In this case the optic nerve was sectioned 1-2 mm in front of the optic chiasm. This was done to spare the theoretical presence of decussating inferonasal fibers from the contralateral optic nerve as they project slightly anteriorly into the opposite optic nerve. This theoretical "knee" is more commonly referred to as Von Wilbrand's knee. It was postulated in 1904 by Herman Wilbrand. He studied cadaveric specimens, which had each suffered a traumatic enucleation at some point during their life. Recent papers have discounted its presence. Lee *et al*. have done living tissue optic nerve resections directly at the chiasm on three separate patients and failed to locate any anteriorly projecting, crossing fibers from the contralateral nerve.[19] Lee *et al*. postulated that the decussating nasal fibers only advance into the contralateral optic nerve after enucleation of the contralteral eye and atrophy of the optic nerve leading to distorted chiasm anatomy and a histological artifact.[19] Horton confirmed this using a monkey model showing that the incursion of the contralateral fibers into the optic nerve occurs gradually over the course of years following monocular enucleation.[12] However, in this case, the patient has been blind for many years secondary to a right retinal hemangioblastoma. It is possible that the right optic nerve has undergone some atrophy resulting in possible histological distortion of the chiasm leading to the presence of the Von Wilbrand's knee in this particular case. Optic tractography is theoretically possible to help identify this anatomical variant; however, no such study has been published.

Table 1: Reported optic nerve hemangioblastomas in the English literature

Author (year)	Age/ Sex	Side	Location	Surgery	VHL
Stefani and Ethoemund (1974)[27]	43M	R	IC	No	No
Lauten *et al.* (1981)[18]	15M	L	IO/IC	Yes	No
Eckstein *et al*. I (1981)[7]	39F	L	IO	Yes	No
In *et al.* (1982)[15]	23F	L	IO	Yes	Yes
Nerad *et al.* (1988)[24]	18F	L	IO	Yes	Yes
Hotta *et al.* (1989)[13]	36M	R	IO	Yes	Yes
Ginzburg *et al.* (1992)[8]	44M	Bil	IC	Yes	Yes
Rubio *et al.* (1994)[26]	43F	R	IO/IC	Yes	Yes
Miyagami *et al.* (1994)[23]	26F	R	IC	Yes	Yes
Kerr *et al.* (1995)[17]	27F	R	IO/IC	Yes	Yes
Raila *et al.* (1997)[6]	30F	L	IC	Yes	Yes
Kato *et al.* (2004)[16]	29M	R	IO/IC	Yes	No
Higashida *et al.* (2007)[11]	64M	L	IO	Yes	No
Meyerle *et al.* (2008)[20]	60F	R	IO	No	Yes
Meyerle *et al.* (2008)[2]	15F	L	IO	Yes	Yes
Meyerle *et al.* (2008)[2]	54M	L	IO	Yes	Yes
Meyerle *et al.* (2008)[2]	29F	L	IC	Yes	Yes
Zywicke *et al.* (2012)[28]	50F	L	IO/IC	Yes	No
Present case	34F	L	IO/IC	Yes	Yes

IO: Intracular, IC: Intracanalicular, VHL:Von hippel-lindau disease

CONCLUSIONS

Optic nerve hemangioblastomas in patients with VHL are rare, but are manageable with meticulous microneurosurgery and with appropriate patient expectations. This is the first known case of an optic nerve hemangioblastoma producing bilateral optic tract edema, which resolved after resection of the prechiasmal tumor. Hemangioblastoma should

remain in the differential diagnosis of optic nerve tumors, especially in the setting of VHL.

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