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Co-occurrence of a cerebral cavernous malformation and an orbital cavernous hemangioma in a patient with seizures and visual symptoms: Rare crossroads for vascular malformations

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Abstract

Background: Cerebral cavernous malformations (CCMs) are angiographically occult vascular malformations of the central nervous system. As a result of hemorrhage and mass effect, patients may present with focal neurologic deficits, seizures, and other symptoms necessitating treatment. Once symptomatic, most often from hemorrhage, CCMs are treated with microsurgical resection. Orbital cavernous hemangiomas (OCHs) are similar but distinct vascular malformations that present within the orbital cavity. Even though CCMs and OCHs are both marked by dilated endothelial-lined vascular channels, they are infrequently seen in the same patient.

Case Description: We provide a brief overview of the two related pathologies in the context of a patient presenting to our care with concomitant lesions, which were both resected in full without complication.

Conclusion: This is the first known report that describes a case of concomitant CCM and OCH and explores the origins of two pathologies that are rarely encountered together in neurosurgical practice. Recognition of disparate symptomatologies is important for properly managing these patients.

Key Words: Cavernous hemangioma, cavernous malformation, orbital hemangioma, orbitotomy

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INTRODUCTION

Cerebral vascular malformations have traditionally been divided into the four categories of (1) arteriovenous malformations (AVMs); (2) cerebral cavernous malformations (CCMs), also known as cavernomas or cavernous hemangiomas; (3) venous angiomas; and (4) capillary telangiectasias, in descending order of incidence. First described by Luschka in 1854, CCMs are benign, low-flow vascular lesions with thin elastic endothelial walls that lack adventitial smooth muscle and frequently present with little intervening

brain parenchyma.[3,29,30,40,47] They account for 10-15% of all cerebral vascular malformations and most often present between the second and fifth decades of life.[6,50] Previous studies estimate the prevalence of cavernous malformations to be 0.4-0.9% in the general population, but up to 50% in some subpopulations with inherited familial syndromes.[14,15,32,39,48,50,67] The majority of cavernous malformations (70-80%) are found supratentorially, 10-20% infratentorially, with the remaining 5-10% in the spine, as visualized by magnetic resonance imaging (MRI).[2,15,47,51,64] The location of intracranial cavernous malformations can be quite ubiquitous, ranging from reported involvement of the third ventricle, lateral ventricle, cavernous sinus, suprasellar region, pineal region, and dura to deeper structures such as the brainstem, thalamus, and basal ganglia.[7,11,17-20,28,33,34,44,57,61,62,65,67] Typically, these lesions remain clinically silent, but depending upon location, size, and potential for mass effect, they have the capability to result in hemorrhage, focal neurologic deficits, and epilepsy. While consensus exists regarding indications for treatment, including increasing neurological deficits, intractable seizures, rapid lesion growth, and control of hemorrhage, considerable debate remains regarding the ideal mode of therapy. A variety of surgical approaches for cerebral vascular malformations have been documented in the literature. Surgical success of these approaches is dependent primarily on the location of the pathology. Deeper-seated lesions, in particular, present a distinct challenge because of the difficulty in gaining access to the malformation and in minimizing the risk of complications from damage to critical anatomical structures.[13] While microsurgical intervention is most common, radiosurgery is controversial, with varying rates of success in the control of lesion growth and prevention of recurrent hemorrhages.[1,4,12,22,37,38,60]

Orbital cavernous hemangiomas (OCHs) are low-flow, angiographically occult vascular malformations that are often considered at the cusp of orbital vascular tumors and orbital vascular malformations.[5] They are distinctly classified as low-flow AVMs in the spectrum of orbital vascular malformations, such as venous malformations, venolymphatic malformations, high-flow AVMs, carotid-cavernous fistula, and aneurysms. Typically well-circumscribed and slow growing, the pathology represents 4-5% of all orbital tumors.[9,58] They are the most common intraorbital primary orbital tumors and the most common orbital vascular lesions in adults.[41,56] OCHs are marked by blood-filled endothelial-lined caverns, which sets them apart from other vascular orbital tumors, such as capillary hemangiomas, hemangiopericytomas, hemangioendotheliomas, and angiofibromas.[5] OCHs lack malignant potential and capacity for endothelial capillary proliferation as seen in pediatric orbital capillary hemangiomas.[42] They are often asymptomatic, but may present with visual symptoms, such as painless ptosis and visual field deficits secondary to compression of the optic nerve. Given the potential of permanent optic nerve dysfunction, current evidence suggests such lesions should be resected as early as possible after diagnosis when patients are symptomatic.[25] Surgical approach is dictated by the location of the lesion within the retroconal space, and possible options may include a lateral zygomatic–frontal orbitotomy (modified Kronlein procedure), transcranial (orbitocranial) approach, or a transconjunctival approach.[54] There have been a number of studies comparing the nature of OCHs with CCMs in terms of pathology and clinical behavior. Hejazi *et al.* have written extensively about the two lesions and conclude that they are clinically, histopathologically, and neuroradiologically different.[23-25] Our report readdresses the questions about the cellular origins of these two neoplasms and highlights the significant histopathology overlap observed in the same patient. While OCHs and intracranial cavernous malformations are common,[2,24,27,49,59,66] to our knowledge, there are no documented reports of co-occurrence of symptomatic cavernous malformation and orbital hemangioma. As such, we herein report a rare case of a concomitant left orbital hemangioma and a cavernous malformation of the left temporo-occipital lobe. These lesions were both symptomatic and resected without complication, resulting in complete resolution of symptoms.

CASE REPORT

A 35-year-old male with a 4-year history of tonic–clonic seizures presented to the emergency room with new-onset headaches, vomiting, and bilateral paresthesias in the hands. Past medical history was significant for congenital glaucoma and a previous left OCH, removed at age 7 via a lateral orbitotomy. His neurologic exam was significant for sluggishly reactive left pupil in addition to mild abducens palsy, esotropia, and mild ptosis of the left eye, consistent with a cranial nerve III and VI palsy. Visual acuity was 20/20 in the right eye and limited to counting fingers with the left eye at baseline. Neuroimaging revealed a 15-mm hemorrhagic mass in the left temporo-occipital region consistent with a CCM and a significant residual left OCH measuring approximately 30 mm [Figure 1a-c]. Given the poor control of seizures despite medication and the epileptogenic potential of the CCM, the patient expressed interest in surgical resection of the left temporo-occipital lesion, but wished to continue with observation of the orbital hemangioma. Benefits and risks of surgical removal of the CCM, with an emphasis on the proximity of the lesion to Meyer's loop and potential for loss of vision, were discussed in full, and the patient consented to the procedure. The mass was successfully resected by left temporal craniotomy without complication. The postoperative

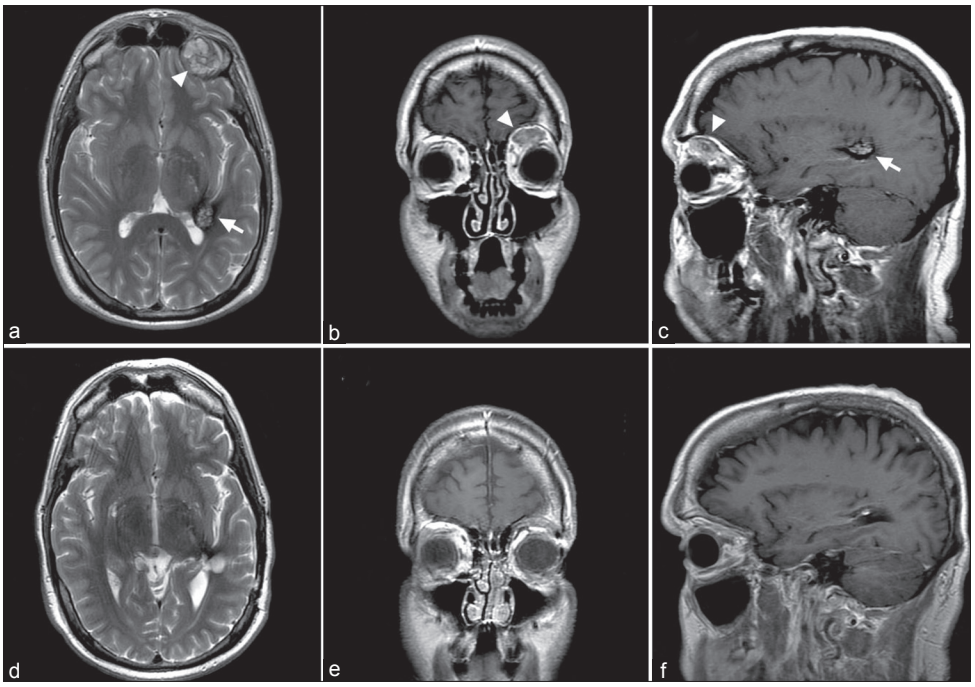

Figure 1: MRI of the CCM and OCH pre- and post-resection (at 3-year follow-up). (a) Axial T2 MRI showing left temporal heterogeneous popcorn lesion (arrow) extending into the atrium of the left occipital horn of the lateral ventricle consistent with a CCM. A left orbital lesion consistent with an orbital hemangioma is also visualized (arrowhead). (b) Coronal T2 image showing OCH. (c) Sagittal T1 image showing the CCM and OCH before resection. (d-f) Axial T2, coronal T2, and sagittal T1 MRIs post-resection demonstrating complete resection of the CCM and OCH

visual field deficits were unchanged. Histopathologic evaluation confirmed the diagnosis of CCM. During biannual follow-up examinations, the patient reported resolution of seizures and successful tapering of his seizure medications. Annual MRI demonstrated stable postsurgical changes. However, at the 3-year follow-up, the patient presented with complaints of supraorbital fullness and an associated sensation of increased ocular pressure of the left orbit. Given these new ophthalmic symptoms, he was referred for oculoplastic ophthalmologic evaluation. Interval MRI demonstrated that the left orbital mass had increased in size, consistent with recurrence of the left orbital tumor that was resected 30 years before [Figure 1]. On examination, his visual acuity in the right eye was 20/20 and in the left eye was limited to counting fingers at 4 feet. Both pupils were reactive to light and accommodation, albeit sluggish in the left eye with a relative afferent pupillary defect. Ocular alignment was notable for a sensory exotropia in the left eye. Examinations of extraocular motility, anterior segment, and dilated fundus of the right eye were all within normal limits. There was notable hypoglobus and severe limitation on supraduction of the left eye. Anterior segment examination of the left eye was significant for blepharoptosis, central corneal haze, and a mild posterior subcapsular cataract. The dilated fundus examination of the left eye revealed marked disc pallor consistent with optic nerve atrophy and retinal vessel dilatation. The patient requested surgical removal of the supraorbital tumor due to the progression of ocular abnormalities and tumor growth. Given the anatomic location of the orbital tumor, the decision was made to perform a left lateral orbitotomy for the removal of the presumed recurrent cavernous hemangioma.

Surgical procedure and follow-up

Following induction of generalized anesthesia, the ophthalmology team made an incision at the upper lid crease and proceeded to dissect superiorly in the plane between the orbicularis muscle and orbital septum [Figure 2]. The superior and lateral orbital rims were then exposed and the periosteum was reflected off the bone. The previous osteotomy sites were identified and an inferior osteotomy was created at the previous surgical site (at the zygomatic arch) using an oscillating saw. A superior marginotomy was then created at the superior orbital rim, medial to the supraorbital notch. The oscillating saw and the craniotome were used to remove the extended bone flap in a single piece of bone. The cutting burr was employed to further conservatively thin the bone in the lateral orbital rim. The branch of the middle meningeal artery anterior to the superior orbital fissure was identified and cauterized. The subperiosteal dissection was continued to the orbital apex to expose the orbital mass in the superior orbit.

Subsequently, the neurosurgical team bluntly dissected around the lesion, which appeared to be most consistent with a recurrent cavernous hemangioma. The feeding

arteries to the lesion were cauterized and cut sharply. The lesion was biopsied and submitted to pathology for frozen and permanent section. The remainder of the lesion was then removed *en bloc* as two specimens. The superior aspect was dissected first followed by the medial and lateral aspects, while the inferior and deep aspects were the final portions to be removed. There were no subsequent post-procedural complications, with visual acuity remaining unchanged from preoperative status. Histopathologic review confirmed the working diagnosis of recurrent OCH [Figure 3]. At his 2-week follow-up, the patient reported complete resolution of supraorbital discomfort. However, he continued to note ptosis of the left eye. Examination demonstrated a diffuse limitation of the extraocular movements secondary to edema, a well-healed upper eyelid incision, and complete ptosis of the left upper eyelid with mild upper lid edema. Six weeks following orbitotomy, visual acuity, ocular motility, and anterior segment examination findings remained stable compared with preoperative status. Over the course of the next several months, the degree of left upper lid ptosis continued to improve, ultimately returning to baseline 6 months postoperatively. At his most recent follow-up examination, 5 years after resection of the intraparenchymal cavernous malformation and 2 years after resection of the orbital hemangioma, the patient's clinical status remains stable. MRI showed typical postsurgical changes at each operative site with no new abnormal signal or enhancement suggestive of recurrence, additional lesions, or hemorrhage [Figure 1d–f].

DISCUSSION

CCMs are low-flow, angiographically occult lesions that often present with seizures, headaches, and focal neurological deficits depending on the location of the malformation. Such lesions can typically be removed microsurgically with a high success rate. The CCM location determines its clinical presentation. Brainstem cavernous malformations can present with cranial nerve palsies and motor or sensory weakness. Similarly, temporal lobe cavernous malformations might present with seizures, as seen in our patient. Kwon *et al.* recently demonstrated a high postoperative long-term seizure-free rate of 82% in patients undergoing resection of cavernous malformations for seizures.[31] In this report, the patient underwent a left temporal approach for resection of the lesion, which placed him at risk of injury to Meyer's loop fibers of the optic radiation in the superior and middle temporal gyri. This is an important consideration with a known large OCH, which can also cause visual field compromise to the patient from optic nerve compression.[45] CCMs have been reported to occur along the optic pathway, such as the optic nerve, optic chiasm, and optic tract, where they can cause visual field disturbances from mass effect.[26] These visual field disturbances should be clinically differentiated from visual compromise caused by OCHs. Several genetic causes of CCMs have recently been identified, with mutations in *KRIT1* (CCM1), *CCM2*, *PDC10* (CCM3), and *RASA1*. Several of these genes are presumed to play roles in endothelial cell interactions with the extracellular matrix, as well as to impact endothelial permeability and proliferation.[10, 63] These syndromes typically show an autosomal dominant inheritance pattern with incomplete penetrance. The genetics behind OCHs, although not fully characterized, suggests that abnormalities of chromosome 13 may be more common in patients with OCH.[53] Potential overlapping genetic loci of OCHs with CCMs need further study and may suggest a common cytogenetic origin given their similarities in histopathology. In terms of histology, these entities show considerable overlap [Figures 3 and 4]. OCHs and CCMs are both marked by dilated vascular spaces lined by endothelium, but have distinct native tissue environments. Both lesions are non-arterial and can show evidence of thrombosis and

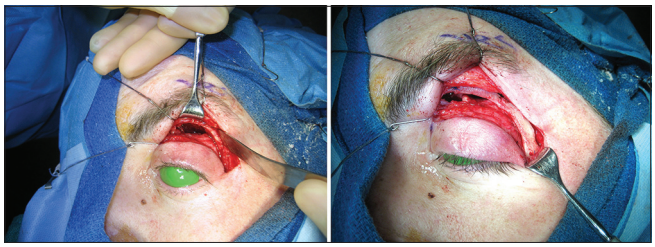

Figure 2: Intraoperative images of the OCH resection. Pathology was resected utilizing an incision along the lid crease. An operative window was created with an extended lateral orbital bone flap

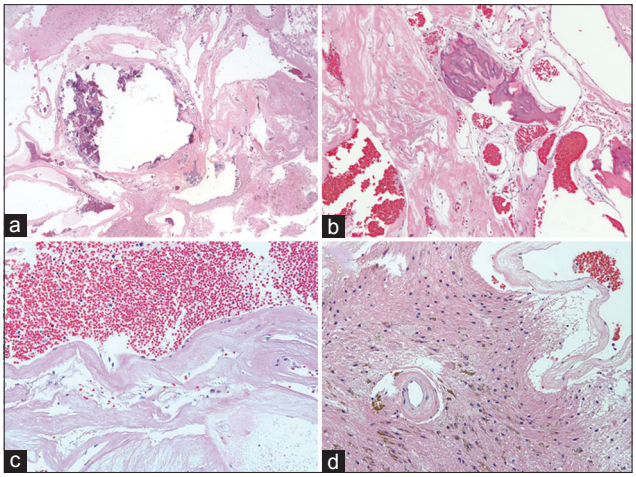

Figure 3: (a, b) CCM comprised cavernous, endothelium-lined vascular sinusoids with foci of calcification (a) and ossification. (b) Little intervening brain tissue between the cavernous vessels was noted. (c) High-power view of the vascular walls of the CCM demonstrates delicate mural hyalinization, scattered extravasated erythrocytes and hemosiderin, and scant inflammation. (d) Brain parenchyma at the periphery of the lesion showing typical hemosiderin deposits, macrophages, axonal spheroids, and gliosis

chronic hemorrhage that is typically marked by the presence of hemosiderin-laden macrophages. Unlike CCMs, OCHs are encapsulated, and though they may have adhesions to the surrounding epimysium of the intraocular muscles, they are non-infiltrative. OCHs are purplish, ovoid lesions with a fibrous pseudocapsule. The abundance of fibrous connective tissue in the surrounding retrobulbar intraconal tissue space allows these lesions to have a clear plane around them, making the resection easier.[21] In contrast, CCMs are soft and mulberry-like with a lack of fibrous trabeculae, causing hemorrhage to extend into the surrounding tissue. A hemosiderin stain in the surrounding brain tissue is often the only margin available to the surgeon when resecting such pathologies. In some scenarios where CCMs are close to the cisternal or ventricular surface, hemorrhage may extend leading to subarachnoid hemorrhage and intraventricular hemorrhage, respectively.[16] Hejazi *et al.* studied the histopathology and radiology characteristics of 19 patients with OCH and compared them with 107 CCMs operated on within the same period.[25] They identified several differences between the two types of cavernous malformations, as highlighted in Table 1, suggesting that these lesions could represent two distinctive lines of differentiation of cavernous lesions. CCMs typically are associated with thin, irregular vascular walls, while rounded, fibrous walls are distinctive of OCHs, suggesting that surrounding tissue plays an important role in the angioarchitecture of these lesions and their presentation. The fibrous capsule of an OCH could represent the orbital fatty tissue reaction to the presence of the hemangioma.[24] Given a different environment in the brain, no such reaction is seen in CCMs; rather, they seem to be associated with developmental venous anomalies (DVAs). DVAs are noted on MRI in up to 25% of patients with CCMs and are hypothesized to be the source of hemorrhagic angiogenic proliferation that predisposes to CCM formation.[46]

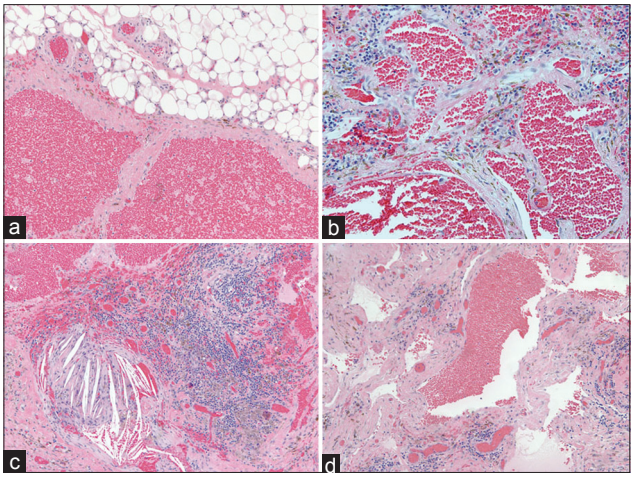

Figure 4: (a) OCH showing a well-circumscribed border with the orbital adipose tissue and a variably thick fibrous capsule. (b) High-power view of the lesion showing cavernous, endothelium-lined vascular sinusoids. Extravasated red blood cells and hemosiderin are noted in between the cavernous sinusoids. In contrast to the CCM, a cellular chronic inflammatory response is seen between the vessels. (c) A focus of organizing hemorrhage with a cholesterol granuloma is shown. (d) An area of the hemangioma showing chronic inflammation and fibrosis between the cavernous sinusoids is seen

Surgical treatment of OCHs is only recommended in symptomatic patients with proptosis, diplopia, pain, decreased visual acuity, or visual field deficits. Surgical resection is safe, and a large number of patients have improvement in symptoms after surgery. The extent of fusion of the OCH capsule with surrounding visually important structures is the most crucial determinant of surgical outcome.[21] Lateral orbitotomy, the most common approach, provides excellent exposure for tumors located in the superior, lateral, or inferior compartment of the orbit. Given that the OCH in our patient was located in the superior compartment, we

Table 1: Comparison of CCM and OCH characteristics

	CCM	OCH
Axial imaging	Rounded contour with clear borders	Focal nodular hyperintensity with calcification
CT	T1: Heterogeneous internally, rim of hypointensity	T1: Homogeneous, isointense to muscle
MRI	T2: Hyperintense T1 post: Non-enhancing	T2: Hyperintense T1 post: Enhancing
Capsule	Hemosiderin rim, no capsule	Encapsulated
Calcification	Present	Absent
DSA	Non-specific; occasional capillary blush, displacement of intraorbital vessels, evidence of neovascularity	
Venous angioma, DVA	Present	Not present
Localization	Orbit (intraconal)	White matter, brainstem, cavernous sinus
Histology	Nonencapsulated aggregate of dilated, variably sized sinusoids (caverns) surrounded by a peripheral rim of gliotic brain with abundant hemosiderin-laden macrophages	Encapsulated, noninfiltrative proliferation of evenly distributed and sized cavernous vascular spaces; no rim of hemosiderin-laden macrophages
Clinical symptomatology	Proptosis, diplopia, impaired acuity, no hemorrhage	Hemorrhage, seizures, neurological deficits, headache

CT: Computed tomography, DSA: Digital subtraction angiography

employed a lateral orbitotomy approach with an extended superolateral bone flap, which resulted in a successful, complete resection.

Extra-axial cavernous hemangiomas rarely occur, comprising 0.5-2.0% of all intracranial vascular malformations.[8,35,36,43,49,52,55] These extra-axial cavernous lesions, of which OCHs are a subset, may occur in soft tissue, skull, orbital cavity, cranial base dura, tentorium, and along nerves. We believe that these cavernous lesions are a spectrum, characterized by endothelial-lined sinusoidal spaces with varying wall thickness and tissue reaction depending upon location.

CONCLUSION

Cavernous vascular lesions can been found in brain and spinal cord tissue as a form of CCMs and in orbital tissue as OCHs. These lesions share many similarities, but maintain distinct characteristics based on the native tissue microenvironment. We present the first case report, to our knowledge, demonstrating a symptomatic CCM and a symptomatic OCH in the same patient with very similar histopathology. Recognition of disparate symptomatologies is important for properly managing these patients.

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