A Review of Cavernous Hemangioma of the Retina and Other Vascular Tumors of the Retina and Choroid

Derek MacDonald, OD, FAAO

ABSTRACT
Vascular tumors of the retina and choroid may be found in isolation or in association with syndromes involving cutaneous and central nervous system lesions. Ophthalmonic lesions may be sight-threatening, and may be the presenting sign of systemic disease with life-threatening consequences. The role of the eye care practitioner in establishing a prompt and accurate diagnosis cannot be understated.

INTRODUCTION
Cavernous hemangioma of the retina is a relatively rare benign vascular tumor typically found unilaterally in Caucasian patients. Its ophthalmonic appearance is quite unique: multiple intraretinal aneurysms filled with venous blood resembling a cluster of grapes projecting above the retinal surface. Intravenous fluorescein angiography demonstrates a pathognomonic pattern of early hypofluorescence and late hyperfluorescence, but no leakage, as fluorescein layers above stagnant red blood cells in each individual aneurysm. As the lesion tends to be stable, regular observation is the rule, unless its location, vitreous hemorrhage, or retinal traction compromise vision.

Differential diagnoses include other vascular tumors or anomalies of the retina or choroid: arteriovenous malformations, Coats’ disease, capillary hemangiomas, vasoproliferative tumors of the retina, and choroidal hemangiomas. Whether sporadic or part of a syndrome, ophthalmonic lesions may be sight-threatening. Associated cutaneous and central nervous system lesions may be life-threatening, making prompt and accurate identification critical. Given that presenting signs and symptoms are often visual, this responsibility may fall upon the eye care practitioner.

VASCULAR TUMORS OF THE RETINA AND CHOROID
Cavernous Hemangioma of the Retina
This is a rare vascular hamartoma, a benign disorganized overgrowth of otherwise normal tissue, typically found unilaterally, primarily in Caucasians.1 4 The average age of onset is the early to mid-twenties, with a slight (60:40) predilection for females.5 These lesions, while most often sporadic, have been classified as part of the phakomatoses, congenital multisystem disorders characterized by the presence of hamartomas in the eye, skin, visceral organs, and central nervous system (CNS).6-11 Defects in the tumor suppression gene resulting in uncontrolled cell growth have been implicated in the formation of these (and other) hamartomas.12

The most common symptoms in patients with CNS lesions include headaches, and seizures and focal neurologic deficits resulting from hemorrhagic stroke and brainstem abnormalities.15-21 Ophthalmonic cavernous hemangiomas have been reported, albeit infrequently, in isolated cases of blue rubber bleb nevus syndrome (BRBNS, previously known as Gascoyen’s syndrome). Lesions of the skin and gastrointestinal tract, causing hemorrhage and anemia typically beginning in infancy, characterize this autosomal dominant (AD) condition, which has been reported in the literature fewer than 200 times. CNS involvement is rare. Differential diagnoses include other conditions associated with vascular skin lesions, including Sturge-Weber syndrome and von Hippel-Lindau disease.22-26

The retinal lesions (Fig. 1) are typically sessile clusters of saccular thin-walled aneurysms within the inner retina filled with dark red venous blood.27-30 Their appearance has been likened to that of a bunch of grapes, and they may be found at any location of the retina, including the optic nerve head (ONH).30 Lesions vary in size, from several disc diameters to those involving multiple quadrants of the fundus.31 There are no prominent vessels feeding or draining the lesion. Growth is rare,
although enlargement of an overlying epiretinal membrane (ERM) and hemodynamic fluctuations in lesion size are possible. An ERM may be absent in lesions involving the ONH.

The aneurysms demonstrate a histologically normal endothelium, maintaining an intact blood/retinal barrier (BRB), and are not typically prone to leakage or intra- or sub-retinal exudation. As such, they usually remain visually asymptomatic unless there is vitreous hemorrhage (VH), retinal traction, or macular involvement. VH is uncommon (<15% of reported cases), although there are reports of labor-induced hemorrhage of cavernous hemangioma of the retina. Optical coherence tomography (OCT) has indicated that, in the absence of trauma and/or Valsalva maneuver, growth and contraction of the ERM is responsible for VH. Progressive thrombosis of individual aneurysms may occur over time.

Given the stability of the majority of these lesions, treatment of an asymptomatic cavernous hemangioma is contraindicated; indeed, there are reports of laser photocoagulation resulting in reduced post-treatment vision secondary to VH, scarring, and retinal traction. Serial fundus photography is recommended. Slow venous perfusion leads to relative stagnation within the hemangioma; gravitational layering of clear plasma atop red blood cells can form a “pseudo-hypopyon” within individual aneurysms. This layering effect can shift with changes in head position. Ultrasonography shows high internal reflectivity (echodense), and intravenous fluorescein angiography (IVFA) demonstrates early hypofluorescence. During the late venous phase, fluorescein slowly trickles into the aneurysms, but does not leak; rather, it pools in the superior plasma, creating a vivid pathognomonic layering appearance that persists long after the dye leaves the rest of the retinal circulation.

This unique IVFA appearance aids in the differential diagnosis versus other vascular tumors/anomalies of the retina and choroid, including:

- Arteriovenous malformations (sometimes in association with Wyburn-Mason syndrome)
- Coats’ disease
- Capillary hemangiomas (sometimes in association with von Hippel-Lindau disease)
- Vasoproliferative tumor of the retina
- Circumscribed or diffuse choroidal hemangiomas (the latter in association with Sturge-Weber syndrome)

### Arteriovenous Malformations of the Retina

Arteriovenous malformations (AVM), previously termed racemose hemangiomas, involve anomalous dilated shunt vessels directly connecting the arterial and venous systems (anastomoses). They are usually found unilaterally (96%), originating at the ONH, although they may also be found in the mid-periphery. The diagnosis may be made at any age. Mild (Group I) cases may remain undiagnosed, whereas moderate (Group II) and severe (Group III) presentations with more extensive arteriovenous anastomoses are usually symptomatic and accompanied by similar malformations in the midbrain and ipsilateral cerebrum as sporadic Wyburn-Mason syndrome. Massively dilated, directly connected arteries and veins demonstrate high-velocity flow of oxygenated blood, and may be indistinguishable from each other in Group III lesions, resembling a “bag of worms” (Fig. 2). While Group I lesions rarely progress, those of Group II and III are prone to exudation, retinal and vitreous hemorrhage, venous occlusion, and secondary neovascular glaucoma; severe vision loss may occur.

IVFA demonstrates abnormal arteriovenous communication, high laminar flow and adjacent capillary dropout. Leakage may be noted secondary to vaso-occlusion. Ultrasonography shows a solid lesion with high internal reflectivity. Intracranial lesions, causing subarachnoid hemorrhage and/or hydrocephalus, typically become symptomatic by age forty. In the presence of ophthalmic lesions, neurologic work-up and imaging are essential. Neither retinal nor intracranial lesions are amenable to therapy.

### Coats’ Disease

First described in 1908, Coats’ disease is not a true neoplasm, but rather a sporadic, unilateral (80 to 95%),
idiopathic, progressive retinal telangiectasia (Fig. 3). It most often affects the inferior and temporal mid-periphery in otherwise healthy young males (4:1 to 10:1 versus females). No ethnic predilection has been identified. In Coats’ disease, the anterior segment remains normal. Some investigators consider it part of a disease continuum including juxtafoveal telangiectasia and Leber’s miliary aneurysms. The latter presents with little if any exudation in the temporal periphery.\textsuperscript{44}

Two pathologic processes are in play: a breakdown of the BRB at the endothelial level and degeneration of the pericytes.\textsuperscript{45} The former causes lipid infiltration into the vessel walls, while the latter leads to aneurysm formation and vessel closure. Significant vision loss results from massive circumferential intra- and sub-retinal lipid exudation; hemorrhage and neovascularization are rare.\textsuperscript{46} Exudative macular/retinal detachment (RD), in the absence of appreciable vitreoretinal traction, occurs in over 80% of cases. Presenting visual acuity is 6/60 (20/200) to no light perception in 76% of cases. Strabismus and leukocoria are common.\textsuperscript{47}

A critical differential diagnosis is retinoblastoma; however, the mean age at diagnosis of Coats’ disease is eleven years, while retinoblastoma typically presents in infancy. IVFA shows capillary non-perfusion, characteristic “light bulb” vascular dilatations and extensive leakage of the telangiectasia in all phases. Ultrasonography demonstrates sub-retinal opacities due to exudation and a linear echo typical of RD.

Treatment in mild to moderate disease aims to minimize exudation and prevent RD through laser or cryo-ablation of the abnormal vasculature. Intravitreal triamcinolone acetonide (IVTA) and anti-vascular endothelial growth factor (anti-VEGF) agents show promise as adjunct therapies. In advanced cases, however, vitrectomy or enucleation may be necessary.

**Capillary Hemangiomas of the Retina**

Capillary hemangiomas of the retina, also known as angiomatosis retinae, hemangioblastomas and hemangiendotheliomas, are benign tumors of the vascular stromal cells. They may occur sporadically (as von Hippel’s disease) or as phakomatoses, the most frequent and earliest manifestation of von Hippel-Lindau (VHL) disease.\textsuperscript{48,49} Bilateral orange-red retinal lesions are found in up to 50% of cases associated with VHL disease. They typically present between the ages of ten and forty and are solitary in two-thirds of cases.

They may be central or mid-Peripheral (the latter is more common, with two-thirds found temporally), and resemble a two- to three-disc diameter coil of capillaries with a single prominent feeding artery and draining vein, even when the tumor is small (Fig. 4). Prominent vessels emanating from the ONH are highly suggestive of a peripheral capillary hemangioma. Juxtapapillary lesions, usually at the temporal ONH margin, may be mistaken for papilledema or peripapillary choroidal neovascularization (CNV), and may lack exaggerated feeding vessels.\textsuperscript{50} Intra-retinal and sub-retinal exudation may remain localized,
but can affect the posterior pole as an “exaggerated macular response” or lead to exudative and/or tractional RD.51

IVFA is an informative ancillary investigation showing significant leakage, unlike cavernous hemangioma of the retina. Long-standing highly exudative lesions can be mistaken for Coats’ disease, although capillary hemangiomas tend to be more discrete, and Coats’ disease lacks prominent feeding/draining vessels. Ultrasonography, demonstrating mid- to high-degree internal reflectivity and sub-retinal fluid, is also helpful in differential diagnosis versus cavernous hemangioma.52 In these and other vascular lesions, fundus autofluorescence (FAF) is increased in the presence of early damage to the retinal pigment epithelium (RPE), and decreased in the presence of RPE death.53 Some advocate prophylactic treatment, given that progressive lesion enlargement and leakage are all but inevitable. Multiple-session laser photo-coagulation, cryotherapy or radiotherapy may be utilized, particularly when tumors are smaller than 4.5 mm. Post-treatment, new lesions are likely to form. While photodynamic therapy (PDT) has proven promising, anti-VEGF injection outcomes have been variable.54,55 During or post-tumor treatment, vitrectomy may be considered in the presence of persistent ERM or tractional macular detachment.56

VHL disease (or cerebelloretinal hemangioblastomatosis) is a rare multiple-system AD familial cancer affecting, at most, 1:36,000 births. It involves renal carcinoma in 40% of patients by age sixty, pheochromocytoma (adrenal gland tumors), pancreatic cysts, and capillary hemangiomas of the eye and CNS, most commonly the cerebellum. Penetrance is age-depandent, and may not be fully realized until the age of sixty-five. It is the only one of the phakomatoses lacking skin lesions and primary involvement of the anterior segment of the eye is uncommon. Retinal lesions are among the most common initial manifestations, found in 95% of patients by age ten.57,58 Given the potential for serious systemic involvement and associated mortality, detection of capillary hemangioma of the retina should trigger prompt medical consultation and, given AD inheritance, examination of other family members.

Vasoproliferative Tumors of the Retina
Vasoproliferative tumors of the retina (VPTR) were first identified in the early 1980s as presumed acquired retinal hemangiomas or localized peripheral adult Coats’ disease. It was thought that they were not true neoplasms, but rare, sporadic, benign peach/yellow elevated proliferations of glial, endothelial, and RPE cells.60 VPTR occur around the age of forty in both healthy men and women as solitary lesions in the far peripheral inferior temporal sensory retina (Fig. 5). In contrast to capillary hemangiomas, feeding vessels are absent or only mildly dilated. As they are very peripheral, some lesions may remain asymptomatic and require only periodic monitoring. Visual acuity, however, is reduced to 6/18 (20/60) or worse 40% of the time. Floaters and photopsia may also be reported.

Surrounding intra- and sub-retinal exudation is found in 75% to 80% of cases and results in extensive fibrous metaplasia of the RPE.61 Eventual exudative RD, remote macular edema (ME) and ERM formation are common. Spectral domain and enhanced depth imaging OCT (SD and EDI OCT) may be helpful in delineating macular changes associated with these, indeed all, vascular tumors. Their anterior location makes imaging studies of the mass itself difficult. However, telangiectatic vessels on and within the lesions have been shown to hyper-fluoresce on wide-field IVFA; ultrasound indicates a solid mass with variable internal reflectivity. Approximately one-quarter of VPTR are secondary to pre-existing
inflammatory/degenerative ocular disease of childhood, including intermediate uveitis, retinitis pigmentosa, Coats’ disease, toxocariasis, toxoplasmosis, and retinopathy of prematurity. Secondary tumors may be bilateral, multiple, and accompanied by anterior chamber and vitreous cells.

Some have hypothesized that these lesions are best classified as a proliferative vitreoretinopathy (PVR) variant. Recent histopathologic investigation has suggested less microvascular and more astrocytic (spindle cell) proliferation. Perhaps VPTR have been inappropriately characterized as non-neoplastic, and are better termed ‘retinal reactive astrocytic tumors’. When treatment is indicated, triple freeze-thaw cryotherapy and laser photocoagulation (for smaller lesions), radiotherapy (for larger lesions), and PDT may be considered. Anti-VEGF agents are being investigated, and while initially promising, no conclusive results are yet available.

**Circumscribed Choroidal Hemangiomas**

In contrast to the retinal lesions already discussed, choroidal hemangiomas are vascular tumors of the uvea. Circumscribed choroidal hemangiomas (CCH) are relatively rare and benign hamartomas not associated with any systemic disease. They typically occur sporadically before the age of forty and may remain asymptomatic for years before causing reduced visual acuity due to sub-retinal fluid. These highly vascular tumors appear as slightly elevated (<6 mm) orange masses posterior to the temporal equator, accompanied by an adjacent exudative or serous RD when symptomatic. There are, however, no prominent feeding or draining vessels (Fig. 6). A pigmented margin may be the only feature distinguishing CCH from the normal adjacent choroid.

Ultrasoundography shows a smooth, discrete, dome-shaped mass with high internal reflectivity. IVFA demonstrates the choroidal origin of the lesion, showing early hyperfluorescence due to a lacy network of intrinsic vessels. Indocyanine green angiography (ICGA), offering increased choroidal visibility, shows late phase “washout” following initial intense hyperfluorescence.

CCH is frequently misdiagnosed. Differential diagnoses include amelanotic choroidal melanoma (more yellow/tan in color, overlying drusen, slower IVFA filling, low internal reflectivity on ultrasonography), choroidal metastases (multiple, creamy yellow lesions), and atypical central serous retinopathy. Treatment, only when symptomatic, may be via aggressive plaque or external beam radiotherapy or laser photocoagulation. The latter is followed by recurrence in 40% of cases. PDT, repeated as required, is preferred for subfoveal CCH due to the fact that it spares the retina and effectively eliminates the sub-renal fluid in 90% of cases. Anti-VEGF injections, both stand-alone and in concert with PDT, are being investigated. Long-duration infrared laser therapy, transpupillary thermotherapy (TTT), is 90% effective for selective destruction of extrafoveal lesions. Regardless of treatment modality, long-term visual prognosis is guarded.

**Diffuse Choroidal Hemangiomas**

Unlike circumscribed lesions, diffuse choroidal hemangiomas (DCH) are part of Sturge-Weber syndrome (SWS, also known as neuro-oculo-cutaneous hemangioma, or encephalotrigeminal or encephalofacial angiomatosis). Unlike other phakomatoses, SWS is not an inherited disorder, but rather a rare, sporadic condition of unknown etiology. It is typified by cutaneous nevus flammeus, or port wine stain, in the dermatome supplied by the ophthalmic (V1) branch of the trigeminal nerve. The lesion rarely involves the maxillary (V2) and mandibular (V3) branches. The congenital dark reddish flat DCH found in nearly 75% of cases of SWS are unilateral, poorly-defined, and ipsilateral to the port wine stain. Given their occasional similarity in appearance to circumscribed choroidal hemangiomas, the presence of a cutaneous lesion is an important differential diagnostic aid.

Although congenital, DCH may not become symptomatic until adolescence through increased hyperopia and/or exudative RD. Ultrasonography demonstrates diffuse, ill-defined choroidal thickening. IVFA shows early and persistent hyperfluorescence; the latter characteristic is unlike circumscribed lesions. Treatment modalities include low-dose radiotherapy, anti-VEGF injection and multifocal PDT.

Vision loss in SWS is usually a consequence of congenital glaucoma ipsilateral to, and strongly associated with, port wine staining of the eyelid. Glaucoma is found in up to 70% of cases, and is typically treated through
multiple, often unsuccessful, filtering procedures. Proposed mechanisms for the insidious elevation of intraocular pressure (IOP) include increased episcleral venous pressure and anterior chamber angle abnormalities, including neovascularization. Affected individuals may also suffer from ipsilateral cerebral venous malformation (parietal and occipital leptomeningeal angiomatosis, the third component of the neuro-oculo-cutaneous triad). This is best visualized through magnetic resonance imaging (MRI) with contrast.73 SWS causes developmental delay, headaches, visual field defects, transient neurologic deficits, and in 80% of patients, contralateral, occasionally intractable seizures within the first two years of life. Pharmacologic anti-seizure treatment may need to be prompt and aggressive; early surgical intervention is controversial.

CONCLUSION
Cavernous hemangioma of the retina is a relatively rare benign vascular tumor, often asymptomatic, typically requiring nothing more than regular monitoring. Treatment is only indicated in the presence of visual compromise resulting from vitreous hemorrhage or macular traction. When associated with neurologic symptoms or cutaneous lesions, neuroimaging is advised.

Differential diagnoses include other vascular tumors or anomalies of the retina and choroid: arteriovenous malformations, Coats’ disease, capillary hemangiomas, vasoproliferative tumors of the retina, and choroidal hemangiomas. In some situations, these ophthalmic lesions are sporadic, while others may be part of the phakomatoses, congenital inherited lesions characterized by the presence of hamartomas in the eye, skin, visceral organs and central nervous system. Given the potential for ocular morbidity and systemic mortality, eye care practitioners play a very important role in early detection and accurate diagnosis.

Acknowledgement: The author gratefully acknowledges the invaluable assistance of Dr. John Gonder in reviewing this manuscript.

REFERENCES