Retinal Vascular Tumors

6

Jose J. Echegaray, Rubens Belfort Neto, and Arun D. Singh

6.1 Introduction

Vascular tumors of the retina generally include four distinct lesions: retinal capillary hemangioma, retinal cavernous hemangioma, racemose hemangioma, and vasoproliferative tumor of the retina. A main differentiation point between these entities arises by classifying them as either congenital in origin or acquired during the lifetime. The congenital retinal vascular tumors include the retinal cavernous hemangioma and the racemose hemangioma. From an ultrastructural standpoint, the vasculature components of these tumors maintain the integrity of endothelial tight junctions throughout life. Clinically, this translates into a lack of exudation or leakage irrespective of the depth of the tumor. In turn, the acquired tumors, retinal capillary hemangioma, and vasoproliferative tumor lack tight junctions and commonly present clinically with an exudative component.

This chapter will discuss the clinical features, diagnostic evaluation, management, and prognosis of the abovementioned tumors with the exception of the vasoproliferative tumor, which will be discussed in Chap. 7. It is important to delineate the differences in clinical presentation and angiographic features between these tumors in order to manage them appropriately.

J. J. Echegaray
Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: echegaj@ccf.org

R. B. Neto
Ocular Oncology Service, Department of Ophthalmology, Federal University of São Paulo, São Paulo, SP, Brazil
e-mail: rubens@belfort.med.br

A. D. Singh (✉)
Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: singha@ccf.org

6.2 Retinal Capillary Hemangioma

6.2.1 Clinical Features

Retinal capillary hemangiomas (RCH) are generally classified based on location (peripheral or juxtapapillary), morphology (endophytic, exophytic, and sessile), its effects on the retina (exudative form and tractional form), and their relationship to von Hippel-Lindau (VHL) disease (with or without VHL disease). Most patients with RCH will present with a solitary tumor, with up to one-third of patients showing multiple tumors. Around 50% of patients will present with bilateral involvement. The association of RCH to VHL is well known with a mean age of presentation of 25 years in those with VHL (Singh et al. 2001). In turn, patients with a RCH that do not have a diagnosis of VHL will present at a later average age of 48 years (Singh et al. 2001).

Typically, a symptomatic patient with a RCH will complain of progressive loss of vision and/or flashes. However, many patients with eccentric lesions may not complain of symptoms and may commonly be diagnosed as an incidental finding in a routine ophthalmic exam. The most common findings on a fundus examination will be of a well-circumscribed, orange-red retinal mass with associated feeder vessels and accompanying lipid exudation (Fig. 6.1). Retinal hemorrhages are only identified in less than 3% of cases (Webster et al. 1999). More commonly, these tumors are located in the temporal quadrants. The finding of engorged retinal vessels arising from the optic disc on ophthalmoscopic view of the posterior pole should arise suspicion for a peripheral RCH and warrant a thorough peripheral examination. In turn, juxtapapillary tumors may not show vessel engorgement in association with the tumor.

The natural history of RCH can vary from spontaneous regression, stability, or progression. Disease progression has been proposed to generally go from early detection of a solitary tumor that may turn into an exudative lesion, which may develop a retinal detachment, and later evolve into end-stage disease with blinding neovascular glaucoma and painful

D. Rojanaporn (ed.), *Ocular Oncology*, https://doi.org/10.1007/978-981-13-2336-2_6

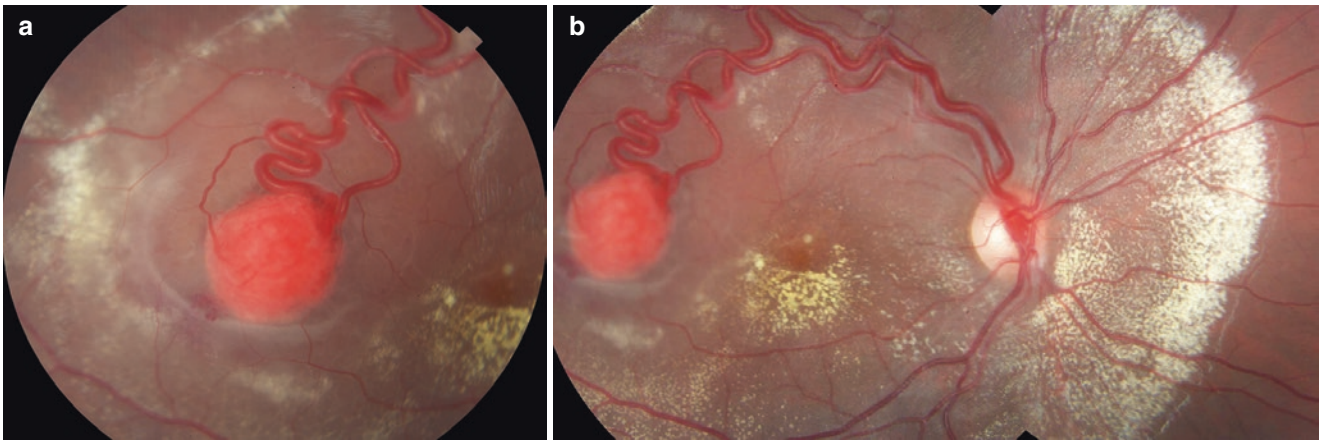

Fig. 6.1 Retinal capillary hemangioma. A well-circumscribed, orange-red retinal mass (**a**). Note prominent feeder vessels and accompanying lipid exudation (**b**)

phthisis. The initial findings at the moment of lesional detection will likely drive the selection of an appropriate treatment regimen.

6.2.2 Diagnosis

In addition to ophthalmoscopy, fluorescein angiography (FA) may aid in the diagnosis of a RCH. The most common findings will be of prominent hyperfluorescence of the tumor in the early stages of the study with associated late leakage. Angiography helps to delineate the tumor margins and provides a map of the tumor feeder vessels by identifying the feeding artery and feeding vein at different stages of the study. This anatomic map facilitates treatment planning.

6.2.3 Management

The appropriate treatment for a RCH is determined by the findings on initial presentation and/or evidence of disease progression, specifically as to the location, size, and presence of subretinal fluid and tractional components. In addition, identifying the presence of multiple tumors and estimating visual potential of the eye are of paramount importance in committing to a treatment plan.

Initial observation may be considered for a RCH, if the solitary tumor is small in size (<500 μm), if there is lack of exudation or tractional retinal detachment, and if there is no threat to the patient's vision. In addition, if the RCH is located in the juxtapapillary region, observation may be a reasonable course of action given the known history of stability of these lesions. Also, a lack of feeder vessels and presence of gliosis in association with the lesion may represent a regressing tumor, for which observation should be employed.

The mainstay of therapy for most RCH is laser photocoagulation (Singh et al. 2001; Singh et al. 2002b). Laser photocoagulation has been reported to be 91% effective when the RCH measures up to 4.5 mm in size and increases to 100% if the tumor is small in size (up to 1.5 mm in diameter) (Singh et al. 2002b). Laser can be employed directly into the tumor or may target a feeder vessel, as indicated by findings on fluorescein angiography. A combination of both, targeting the tumor and its feeder vessel, is another alternative. The resolution of fluid, tumor shrinkage, or change in color from red to pale pink generally represents therapeutic response and clinical resolution without the need to achieve complete tumor obliteration.

When the RCH is located anteriorly, if the tumor measures more than 3.0 mm in size, or if there is presence of moderate amount of subretinal fluid that may limit laser intake, cryotherapy may be an appropriate option (Singh et al. 2002b). As with laser photocoagulation, cryotherapy is most effective when the tumor measures less than 1.5 mm in diameter. Cryotherapy is not recommended when the tumor is juxtapapillary. Recently, there have been reports of successful treatment of RCH with photodynamic therapy by inducing occlusion of peripheral and juxtapapillary lesions (Schmidt-Erfurth et al. 2002; Bakri et al. 2005; Sachdeva et al. 2010). However, it was reported that visual stabilization or improvement was only present in half of cases with worsening epiretinal membranes in up to a half of cases, requiring further surgery (Sachdeva et al. 2010).

Episcleral plaque brachytherapy is another tool in the arsenal to treat RCH that are greater than 4 mm in size and show poor response to cryotherapy and laser photocoagulation (Singh et al. 2001; Singh et al. 2002b). The reported mean apical dose for RCH when treated with Iodine-125 plaque is 34 Gy prescribed to the apex of the lesion (range 22 Gy–41 Gy) (Singh et al. 2002b). Low-dose external beam

radiotherapy has also been reported as rescue therapy in recalcitrant cases (Raja et al. 2004). Intravitreal anti-VEGF therapy may serve as an adjuvant therapy to reduce exudation in combination of laser photocoagulation or cryotherapy, especially in cases of juxtapapillary RCH and small peripheral lesions (Slim et al. 2014). However, anti-VEGF monotherapy has not been shown significant benefits on the RCH size per se (Wong et al. 2008). For eyes with secondary tractional retinal detachments or total exudative detachments, pars plana vitrectomy with possible endodiathermy or endophotocoagulation of feeder vessels may serve to stabilize these cases (Avci et al. 2017).

6.2.4 Systemic Associations

It is well known that RCH is associated with Von Hippel-Lindau (VHL) disease, a syndrome that commonly manifests with vascular tumors in the retina and the central nervous system (CNS). Since RCH is the most common initial manifestation in VHL patients, knowing how to diagnose this condition is of paramount importance to every ophthalmologist. Additional systemic manifestations include cerebellar hemangiomas, renal cell carcinoma, and pancreatic tumors and cysts. Examination of these patients should be extended into immediate relatives, given its association with the VHL gene on chromosome 3p2526 and autosomal dominant inheritance (Stolle et al. 1998; Singh et al. 2002a). Genetic testing for VHL gene is commercially available.

6.3 Retinal Cavernous Hemangioma

6.3.1 Clinical Features

Cavernous hemangioma of the retina (CHR) is considered a rare form of congenital retinal hamartoma that is commonly sporadic and of equal gender distribution (Wang and Chen 2017). However, a subset of patients has shown an autosomal dominant hereditary pattern in association with cerebral cavernous malformations. The age of presentation has been reported to range between 1 and 55 years of age, with recent reports showing that 70% of cases present between 7 and 40 years of age with a mean age of presentation of 21 years (Messmer et al. 1983; Wang and Chen 2017). Ophthalmoscopically, CHR appear as peripheral solitary clusters of grape-like saccular thin-walled channels with associated retinal gliosis (Fig. 6.2). These tumors are usually small in size, measuring approximately 1–2 disc diameters. Ultrastructurally, the saccular channels are lined by non-fenestrated endothelium, which explains the lack of exudation evident on clinical exam. Another characteristic clinical feature of CHR is its independence from

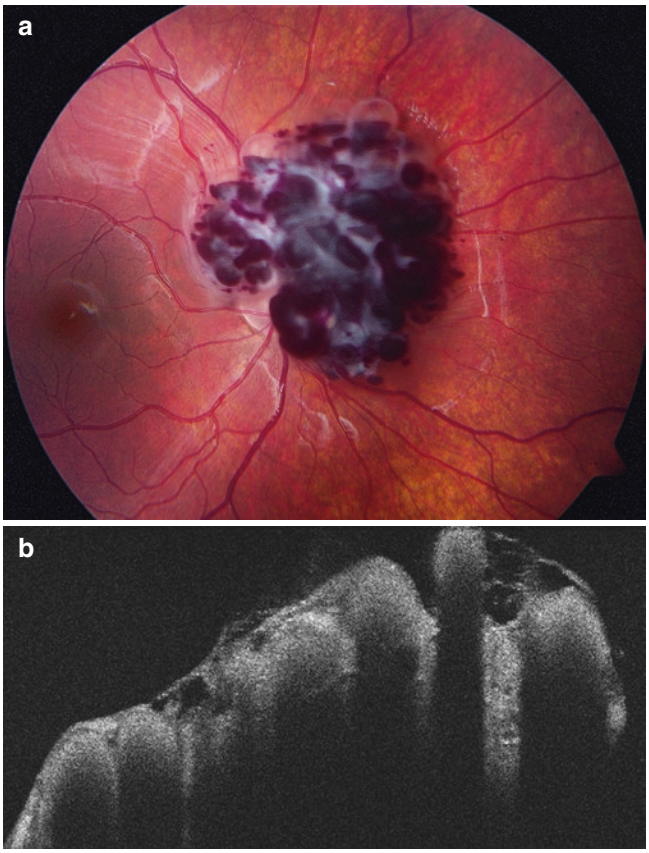

Fig. 6.2 Retinal cavernous hemangioma. A cluster of grape-like saccular vascular channels (**a**) that are thin walled when examined by OCT (**b**)

the surrounding retinal circulation, evident by the relatively unaffected retinal vasculature overlying and surrounding the lesion and the lack of any feeder vessels. Patients with CHR are generally asymptomatic. Those with visual complaints usually involve the macula or have associated vitreous hemorrhage.

6.3.2 Diagnosis

Fluorescein angiography can aid in the diagnosis of CHR with a relatively early hypofluorescence and delayed lesional dye filling, representing the low-flow system of the cavernous vascular channels. In the venous phase of the study, hyperfluorescent caps may be evident within the saccular channels, representing gravitational plasma-erythrocytic separation. There is a lack of fluorescein leakage, consistent with the non-fenestrated vascular channels that form these tumors. OCT scan through the tumor may illustrate preretinal and epiretinal membranes that form bridges between the saccular channels (Pringle et al. 2009). Contraction of these membranes is believed to cause subretinal or vitreous hemorrhage, which has been reported in 25% of cases (Wang and Chen 2017).

6.3.3 Management

Generally, patients with CHR are observed since most are asymptomatic and the tumors are generally non-progressive with a lack of exudation that would otherwise cause vision loss. Those that progress may show an increase of gliosis and thrombosis.

6.3.4 Systemic Associations

Although most cases of CHR are sporadic, few cases have been associated with a familial syndrome in association with cerebral cavernous hemangiomas. It has been suggested that bilateral CHR cases strongly correlate with familial history (Wang and Chen 2017). Patients with cerebral hemangiomas may warrant close follow-up, due to the possibility of seizures, intracranial hemorrhages, and death (Dobyns et al. 1987; Wang and Chen 2017).

6.4 Racemose Hemangioma

6.4.1 Clinical Features

Racemose hemangiomas (Wyburn-Mason syndrome) are sporadic congenital arteriovenous malformations that are usually identified incidentally in ophthalmoscopic examination in asymptomatic patients or in children with amblyopic eyes. The average age of presentation has been reported to be 23 years (Qin et al. 2014). Ophthalmoscopy discloses vascular malformations subdivided according to severity (Fig. 6.3). Group I features major vessels of the arteriovenous malformation joined by a capillary plexus. Group II lesions lack the intermediate capillary plexus. Group III is the most severe having significant dilation and tortuosity of the malformed vasculature. There is usually a lack of lipid exudation or retinal feeder vessels. Over time, these lesions may show an increase in tortuosity, vessel occlusion, and ischemia with subsequent development of neovascular glaucoma (Augsburger et al. 1980).

6.4.2 Diagnosis

Fluorescein angiography illustrates the arteriovenous malformation and may aid in further classifying the lesion by identifying the presence or absence of an intervening capillary plexus. A lack of differentiation between the arterial and venous components of the malformation on angiography is characteristic of group III lesions.

6.4.3 Management

Retinal arteriovenous malformations are generally not treatable. Secondary complications such as vitreous hemorrhage or neovascular glaucoma may be treated accordingly.

6.4.4 Systemic Associations

The association of racemose hemangioma with cerebral arteriovenous malformations has been established as Wyburn-Mason syndrome. Approximately 30% of patients with retinal manifestations also have concomitant cerebral involvement

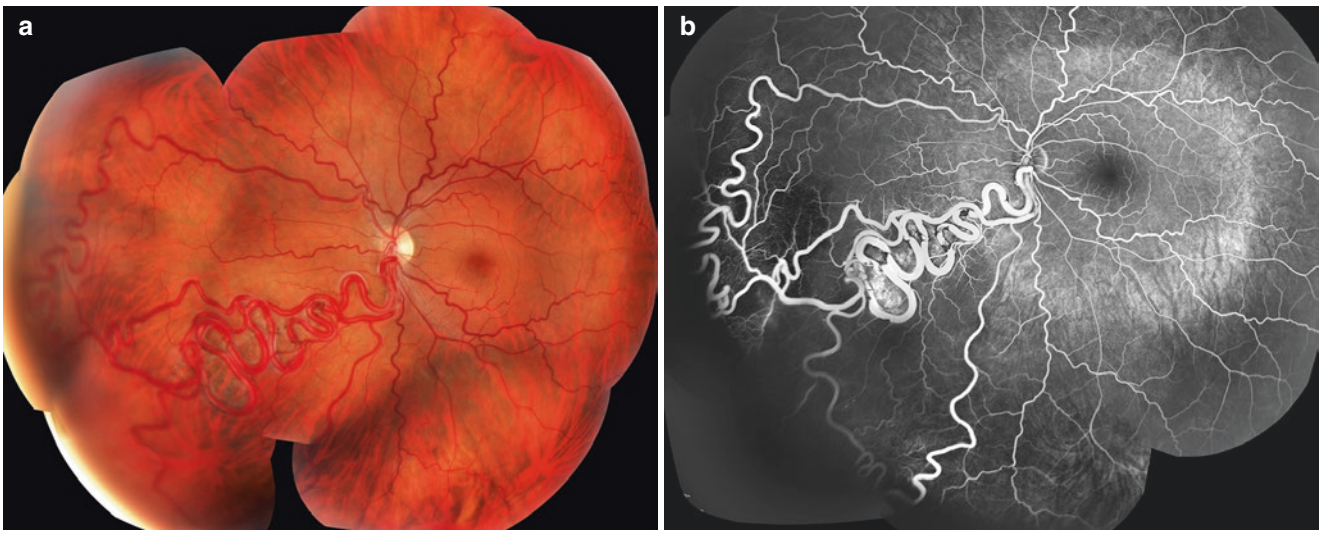

Fig. 6.3 Racemose hemangioma. Retinal arteriovenous malformation lacking intermediate capillary plexus (**a**). The vessels maintain endothelial tight junctions as suggested by absence of leakage on fluorescein angiogram (**b**)

(Ponce et al. 2001). Intracranial malformations involving the optic chiasm may present with neuro-ophthalmic manifestations. Associated cerebral hemorrhages may present with symptoms such as headaches, nuchal rigidity, or loss of consciousness. Patients identified with retinal arteriovenous malformation by an ophthalmologist should be evaluated for early detection of concomitant cerebral malformations.

References

Augsburger JJ, Goldberg RE, Shields JA, et al. Changing appearance of retinal arteriovenous malformation. Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie Albrecht Von Graefes. Arch Klin Exp Ophthalmol. 1980;215:65–70.

Avci R, Yilmaz S, Inan UU, et al. Vitreoretinal surgery for patients with severe exudative and proliferative manifestations of retinal capillary hemangioblastoma because of von hippel-lindau disease. Retina. 2017;37:782–8.

Bakri SJ, Sears JE, Singh AD. Transient closure of a retinal capillary hemangioma with verteporfin photodynamic therapy. Retina. 2005;25:1103–4.

Dobyns WB, Michels VV, Groover RV, et al. Familial cavernous malformations of the central nervous system and retina. Ann Neurol. 1987;21:578–83.

Messmer E, Laqua H, Wessing A, et al. Nine cases of cavernous hemangioma of the retina. Am J Ophthalmol. 1983;95:383–90.

Ponce FA, Han PP, Spetzler RF, et al. Associated arteriovenous malformation of the orbit and brain: a case of Wyburn-Mason syndrome without retinal involvement. Case report. J Neurosurg. 2001;95:346–9.

Pringle E, Chen S, Rubinstein A, et al. Optical coherence tomography in retinal cavernous haemangioma may explain the mechanism of vitreous haemorrhage. Eye (Lond). 2009;23:1242–3.

Qin XJ, Huang C, Lai K. Retinal vein occlusion in retinal racemose hemangioma: a case report and literature review of ocular complications in this rare retinal vascular disorder. BMC Ophthalmol. 2014;14:101. https://doi.org/10.1186/1471-2415-14-101.

Raja D, Benz MS, Murray TG, et al. Salvage external beam radiotherapy of retinal capillary hemangiomas secondary to von Hippel-Lindau disease: visual and anatomic outcomes. Ophthalmology. 2004;111:150–3.

Sachdeva R, Dadgostar H, Kaiser PK, et al. Verteporfin photodynamic therapy of six eyes with retinal capillary haemangioma. Acta Ophthalmol. 2010;88(8):e334–40. https://doi.org/10.1111/j.1755-3768.2010.02008.x.

Schmidt-Erfurth UM, Kusserow C, Barbazetto IA, et al. Benefits and complications of photodynamic therapy of papillary capillary hemangiomas. Ophthalmology. 2002;109:1256–66.

Singh AD, Shields CL, Shields JA, et al. von Hippel-Lindau disease. Surv Ophthalmol. 2001;46:117–42.

Singh AD, Ahmad NN, Shields CL. Solitary retinal capillary hemangioma: lack of genetic evidence for von Hippel-Lindau disease. Ophthalmic Genet. 2002a;23:21–7.

Singh AD, Nouri M, Shields CL, et al. Treatment of retinal capillary hemangioma. Ophthalmology. 2002b;109:1799–806.

Slim E, Antoun J, Kourie HR, et al. Intravitreal bevacizumab for retinal capillary hemangioblastoma: a case series and literature review. Can J Ophthalmol. 2014;49:450–7.

Stolle C, Glenn G, Zbar B, et al. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. Hum Mutat. 1998;12:417–23.

Wang W, Chen L. Cavrnous hemangioma of the retina: a comprehensive review of the literature (1934-2015). Retina. 2017;37:611–21.

Webster AR, Maher ER, Moore AT. Clinical characteristics of ocular angiomatosis in von Hippel-Lindau disease and correlation with germline mutation. Arch Ophthalmol. 1999;117:371–8.

Wong WT, Liang KJ, Hammel K, et al. Intravitreal ranibizumab therapy for retinal capillary hemangioblastoma related to von Hippel-Lindau disease. Ophthalmology. 2008;115:1957–64.