Ocular Von Hippel-Lindau Disease

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Von Hippel-Lindau (VHL) disease is an autosomal dominant, multisystem disorder with a predilection for the central nervous system (CNS) and the retina. The incidence of VHL disease is approximately 1 in 40,000 to 1 in 54,000 live births [1]. Retinal capillary hemangioblastoma is the most common and often the earliest manifestation of VHL disease [2]. Therefore, ophthalmologists play a crucial role in the early diagnosis and management of these patients.

10.1 History

Eugen von Hippel, a German ophthalmologist, coined the term angiomatosis retinae in 1904 which later came to be known as retinal hemangioblastoma (retinal hemangioma) [3]. Lindau, a Swedish pathologist, established the relationship between cerebellar and retinal hemangioblastomas. In 1964, Melmon and Rosen reported cases of "von Hippel's disease" and "Lindau's disease" with overlapping ophthalmic, CNS, and visceral manifestations, establishing the clinical spectrum of "von Hippel–Lindau" disease [4].

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10.2 Ophthalmic Manifestations

Retinal capillary hemangioma, a slow growing benign hamartoma, is the most common and earliest presentation in VHL. The mean age at diagnosis of retinal capillary hemangioma in VHL disease is 25 years and most patients present between their 10th and 40th years [5, 6]. The frequency of occurrence of retinal capillary hemangioma in VHL disease has been reported to vary from 49% to 85% [7–9]. It usually manifests as a solitary tumor but one-third of patients have multiple hemangiomas [10]. Half of the patients have bilateral involvement [11].

Retinal capillary hemangiomas are usually orange-red circumscribed, round vascular tumors supplied by a pair of dilated and tortuous feeder vessels (Fig. 10.1).

They can be asymptomatic. In cases with exudation, they can present with diminution of vision or metamorphopsia. They can be classified (Table 10.1) based on the location, morphology, effects on the retina and relationship to VHL disease [12, 13].

Most of the retinal capillary hemangiomas are in the temporal periphery and accompanied by at least one pair of dilated retinal vessels [2, 14, 15]. Juxtapapillary retinal capillary hemangiomas are less common (11–15% of cases) and their appearance can vary depending on whether the lesion is endophytic, exophytic or sessile. The endophytic variant appears as an orange red protrusion from the anterior surface of the optic disk and adjacent

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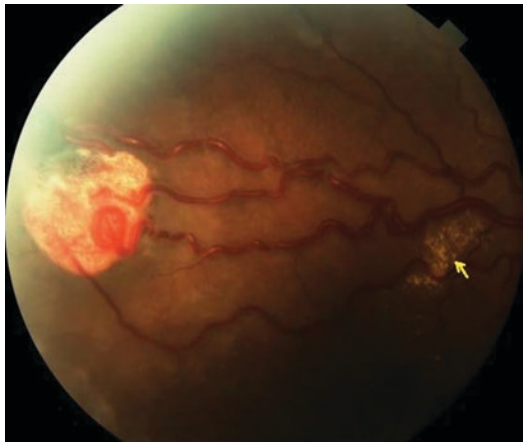

Fig. 10.1 Fundus photograph showing a round orange retinal lesion with prominent dilated retinal vessels typical of retinal capillary hemangioma. Note the presence of exudation (arrow)

Table 10.1 Classification system for retinal hemangioma [3]

Basis	Classification
Retinal distribution	1. Peripheral 2. Juxtapapillary 3. Bilateral
Effects of retina exudative	a. Vascular dilation/ exudation b. Retinal detachment c. Vitreoretinal traction
Systemic involvement	L-. Without VHL L+. With VHL

retina [2]. The exophytic tumor is adjacent to or surrounding the optic disk and can simulate chronic papilledema [2]. The sessile variant of juxtapapillary retinal capillary hemangioma is subtle in appearance and can be difficult to diagnose [2].

Secondary effects are predominantly exudative (25%) or tractional (9%) [2]. Intraretinal and subretinal exudation are limited to the vicinity of the hemangioma, but can also produce a macular star exudate leading to visual deterioration. Secondary glial proliferation on the retina and in the vitreous can lead to tractional retinal detachment [2]. The anterior segment is rarely involved secondarily with complications such as neovascular glaucoma and cataract.

10.3 Natural History of Disease

The retinal capillary hemangioma probability increases progressively with age. Classification systems aiding in staging the clinical progression have been developed by Vail [16].

The natural course of retinal capillary hemangiomas can be either of progression, stability or spontaneous regression [5]. Small lesions may remain stable for years, may show gliosis without leakage, or enlarge. In late stage, they may cause massive exudation and retinal detachment, uveitis, neovascular glaucoma and phthisis bulbi.

10.4 Differential Diagnosis (Table 10.2)

The fundus findings of retinal capillary hemangioma are typically diagnostic and can be observed during ophthalmoscopic examination. However, the following conditions should be ruled out:

Coat's Disease: Intraretinal exudation and collection of subretinal fluid is present, both, in Coat's disease and retinal capillary hemangioma. The vascular abnormality, however, is diffuse in Coats's and localized in retinal capillary hemangioma. Prominent feeder vessels, circumscribed round retinal angioma, family history and systemic features of VHL disease are also absent [2].

Wyburn–Mason Syndrome (Racemose Angioma): The dilated vessels of racemose angioma do not have an intervening orange red circumscribed retinal capillary hemangioma. They do not leak blood, serum or exudate.

Retinal Cavernous Hemangioma: This is a cluster of small, saccular vascular dilations around a central vein, but there are no prominent feeder vessels or exudation.

Retinal Macroaneurysm: Presents with subretinal, intraretinal or vitreous hemorrhage. It is centered on a retinal arteriole and feeder vessels are absent. There is often a history of systemic hypertension.

Vasoproliferative Tumor: Presents with retinal capillary hemangioma, orange color and presence of exudation. The differentiating feature is the absence of prominent feeder vessels and extreme peripheral retinal location of VPRT.

Astrocytic Hamartoma: Prominent vascularity makes the differentiation from retinal capillary hemangioma difficult. However, astrocytic hamartoma

Table 10.2 Diagnostic features of retinal vascular tumors

Type	Location	Appearance	Feeder vessels	Exudation
Retinal capillary hemangioma	Juxtapapillary/ peripheral	Round reddish mass	Prominent	Present
Coat's disease	Peripheral	Irregular dilatations with telangiectasia	Absent	Present
Cavernous hemangioma	Non-specific	Saccular grape like clusters	Absent	Absent
Racemose angioma	Diffuse	Dilated tortuous retinal vessels	Absent	Absent
Vasoproliferative tumor	Periphery	Orange globular mass	Absent	Present
Retinal macroaneurysm	Posterior	Round red lesion	Absent	Present
Astrocytic hamartoma	Posterior pole	Translucent or white mass	Absent	Usually absent

is usually translucent, does not have feeder vessels and is calcified.

Others: RPA adenoma or uveal melanoma with prominent feeder vessels can sometimes resemble capillary hemangioma. Juxtapapillary retinal capillary hemangioma can also simulate unilateral disc edema, juxtapapillary choroiditis, choroidal neovascularization, choroidal hemangioma and amelanotic choroidal melanoma.

10.5 Diagnostic Methods

Fluorescein angiography is the most informative diagnostic tool to detect retinal capillary hemangioma. Due the vascular nature of the tumor and endophytic growth pattern it exhibits a dramatic and relatively unique pattern of hyperfluorescence [17]. Obtaining early-phase images is critically important. Fluorescein is evident in the early arterial phase in the dilated feeder arteriole, the tumor has fine capillary homogeneous filling, and the draining vein becomes prominent in the venous phase. The tumor demonstrates progressively intense hyper-fluorescence with late leakage of dye into the overlying vitreous humor (Fig. 10.2). Fluorescein angiography is helpful in establishing the diagnosis of juxtapapillary hemangioma and can be an adjunct to treatment planning by differentiating the feeder arteriole from the draining vein. Fluorescein angiography is particularly helpful for assessment of the tumor's response the treatment.

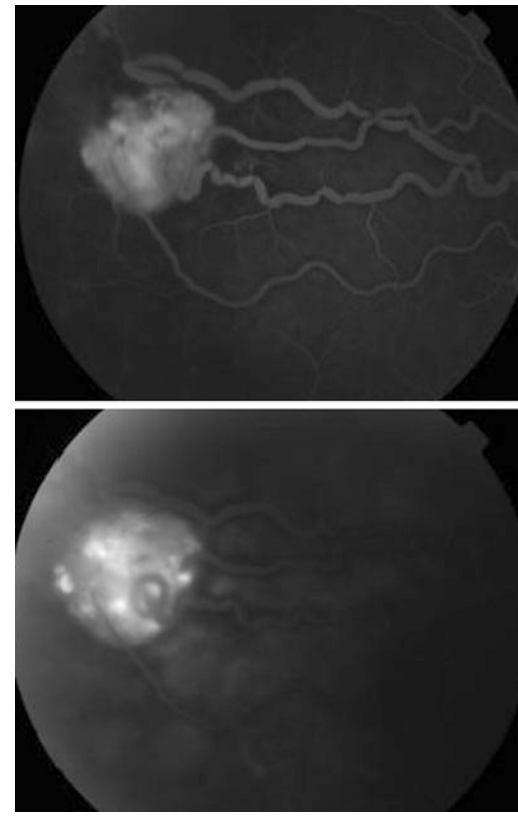

Fig. 10.2 Fluorescein angiogram demonstrating (top) progressive and complete filling of the hemangioma, retinal artery and the vein and (bottom) late leakage of the retinal capillary hemangioma

Other diagnostic modalities may be employed but have a minimal role. ICG can help differentiate choroidal lesions, such as choroidal hemangioma or choroidal neovascular membrane from retinal capillary hemangioma [2, 18].

Ultrasonography can help measure the tumor thickness. A-scan shows an initial spike followed by high internal reflectivity and B-scan shows a well-demarcated retinal lesion without choroidal invasion [19]. If present, B-scan can also document secondary exudative retinal detachment.

MRI can detect associated CNS hemangiomas. Color Doppler imaging and laser scanning tomography can be used to document tumor blood flow and angiographic changes in feeder vessels after treatment [2, 20].

10.6 Treatment

Treatment depends upon the location, size and related complications, presence of bilateral multiple tumors and the likelihood of new tumor formation. Despite treatment, 25% of patients show permanent visual loss (vision of 20/40 in one or both eyes) and 20% have visual acuity less than 20/100 in at least one eye [2].

Treatment modalities include observation, cryotherapy, plaque radiotherapy and vitreoretinal surgery. Understanding of VHL protein function and tumorigenesis have led to new treatment that target the biology of the disease, as opposed to ablative or surgical approaches. Molecules upregulated in the VHL mutation, such as VEGF and PDGF, have been targeted in investigational anti-angiogenic therapies, both in systemic and ocular manifestation of the disease [10].

10.6.1 Observation

It can be considered if the retinal capillary hemangioma is very small (up to 500 microns), not associated with exudation, does not threaten the vision or has undergone spontaneous regression with gliosis, sheathing and lack of feeder vessels [2]. Juxtapapillary hemangiomas are more commonly treated with primary observation in that they can remain stable for years. Treatment should only be taken when tumor progresses or causes a threat to visual acuity, due to the adverse effect of treatment on the optic nerve and major vessels [13, 21].

10.6.2 Laser Photocoagulation

To treat small to medium-sized retinal capillary hemangiomas in eyes with clear media. At The New York Eye Cancer Center, we typically first close the arterial feeder vessel(s). If such indirect tumor devascularization is not achieved, we encircle the posterior 180° of the tumor to avascular scar. If complete vascular regression has still not been achieved, then we apply laser directly to the hemangioma (Fig. 10.3). A response rate of 91–100% has been shown with laser treatment [22, 23]. In general, response to laser treatment is evaluated in 4–6-week intervals (Fig. 10.4).

10.6.3 Cryotherapy

Anterior location of the hemangioma, subretinal fluid which can reduce the laser energy uptake and diameter greater than 3 mm are indications of cryotherapy. Double freeze-thaw technique is employed under indirect ophthalmoscopy [5]. The cryotherapy is applied until the ice ball completely encloses the hemangioma before thawing is initiated [2]. A 15-year review found that all hemangiomas under 3.75 mm in diameter successfully responded to cryotherapy. However, there is a risk of cryotherapy-related exudative detachment.

10.6.4 Plaque Brachytherapy

A recent study proved that plaque treatment was efficacious for retinal capillary hemangiomas that were 5 mm or less in diameter [2]. Radiation complications can be related to tumor location and radiation dose to the fovea and optic nerve [24, 25].

10.6.5 Anti-Angiogenic Medications

Drugs like bevacizumab and ranibizumab, have been used, but do not provide long-term cessation of tumor growth or reduction in subretinal fluid

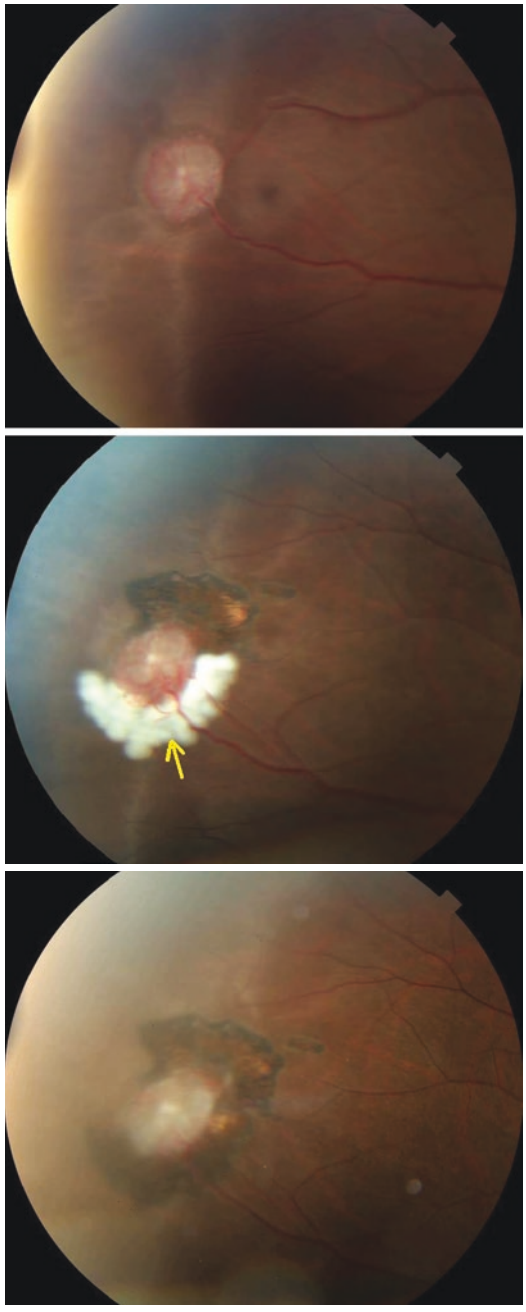

Fig. 10.3 Fundus photograph showing (top) retinal capillary hemangioma measuring 2.0 × 2.0 mm in size before and (middle) immediately after placement of photocoagulation on the feeding artery delimiting the lesion. Argon green laser was used with spot size of 250–500 microns, duration of 0.20 s, and power of 250–500 mW. Total of 200 spots (arrow) were applied. (Bottom) Delineated stable lesion after 6 weeks of treatment

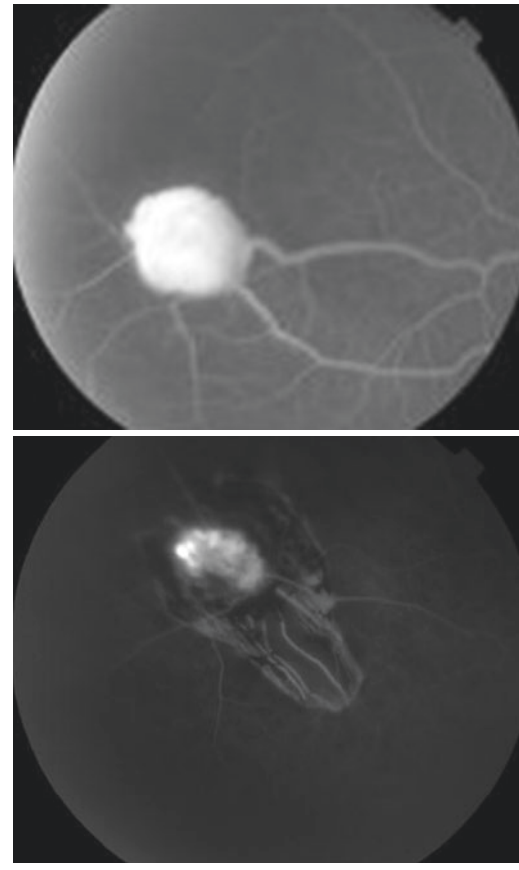

Fig. 10.4 Fluorescein angiogram (top) prior to treatment with laser photocoagulation and (bottom) 6 weeks after treatment. Note the presence of sclerosed vessels

[26–28]. A prospective study of intravitreal pegaptanib, an aptamer that inhibits VEGF isoform 165, found that pegaptanib did not influence lesion regression, but can minimally decrease exudation in some cases [29]. A small case series of oral propranolol was studied in 7 patients, the hemangiomas showed stability of the lesions during treatment [28].

10.6.6 Others

Transpupillary thermotherapy (TTT), photodynamic therapy, proton beam radiation have also been described with inconsistent results. Pars plana vitrectomy may become necessary for

advanced and complicated cases [5]. Enucleation is performed for blind-painful eyes unresponsive to conservative therapy.

10.7 Systemic Manifestations

The systemic manifestations of VHL include CNS hemangiomas of the brain and spinal cord, renal cell carcinomas, renal cysts, pheochromocytomas, pancreatic cysts, islet cell tumors, epididymal cystadenomas, endolymphatic sac tumors of the inner ear and adnexal papillary cystadenomas of the broad ligament [30]. About 50% of VHL patients manifest only one feature of VHL disease, and very few develop all the manifestations [2, 8]. After retinal capillary hemangioma, the most frequently affected organ systems are the CNS, kidneys and adrenal glands, many of them occurring years after the initial presentation with retinal capillary hemangiomas [30].

The diagnosis of VHL disease is based on retinal capillary hemangioma or CNS hemangioma, visceral lesions and a family history of similar lesions (Table 10.3). After the diagnosis is made, both ophthalmic and systemic screening protocols should be followed. At The New York Eye Cancer Center, we perform brain and abdominal imaging at diagnosis and every 2 years thereafter.

Table 10.3 Diagnostic criteria for von Hippel-Lindau disease [2]

Family history	Features
Positive	Any one of the following: 1. Retinal capillary hemangioma 2. CNS hemangioma 3. Visceral lesions[a]
Negative	Any one of the following: 1. Two or more retinal capillary hemangiomas 2. Two or more CNS hemangiomas 3. Single retinal or CNS hemangioma with a visceral lesion[a]

[a]Visceral lesions include renal cysts, renal carcinoma, pheochromocytoma, pancreatic cysts, islet cell tumors, epididymal cystadenoma, endolymphatic sac tumor, and adnexal papillary cystadenoma

Initial and yearly medical physical, neurologic examinations are obtained.

According to National Cancer institute, VHL disease can be classified, on clinical grounds, into two main types: Type I (pheochromocytoma absent) and Type II (pheochromocytoma present) [2].

10.8 Genetics

VHL disease is an autosomal dominant disease, due to heterozygous mutation of VHL tumor suppressor gene located on chromosome 3p25-26. The protein product of the VHL gene forms a complex with other proteins that targets hypoxia inducible factors (HIFs) for degradation. Mutations in the VHL gene result in stabilization of the HIFs, which bind to specific enhancer in elements in the VEGF gene and stimulate angiogenesis.

Patients with a suspicion or diagnosis of VHL should undergo both genetic testing and counseling. With a near complete penetrance of the disease, genetic testing has been proven to be helpful in early diagnosis and clinical screening for disease manifestations.

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