Dramatic Retinal Lesion in Asymptomatic 15-Year-Old Female

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Introduction:

A 15-year-old female presented for examination to screen for a retinal condition. She did not have any visual complaints. She was born full-term and was otherwise healthy. She denied medication, tobacco, alcohol, or drug use. Her 45-year-old mother had recently been admitted to the hospital and was diagnosed with Renal Cell Carcinoma. Following genetics consultation, the patient and her 13-year-old brother were referred for examination.

Visual acuity measured 20/20 OU. There was no relative afferent pupillary defect. The intraocular pressure and anterior segment exam tion were normal.

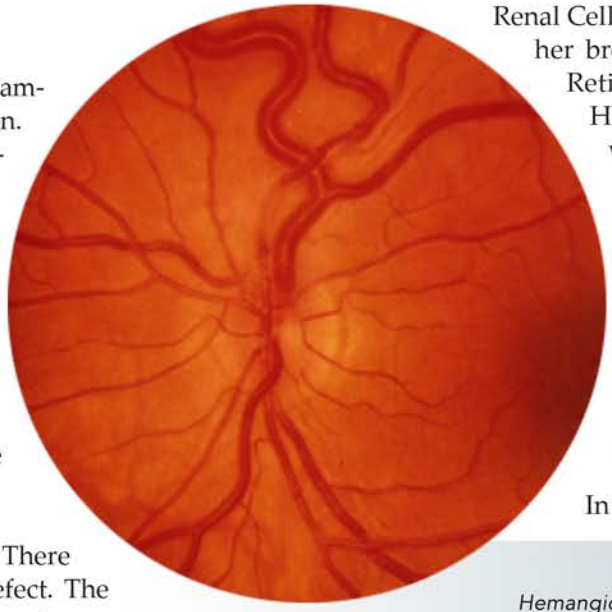
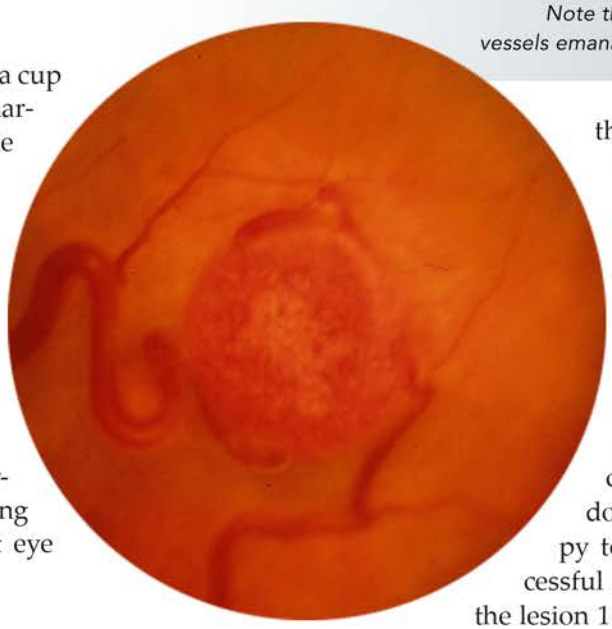


Figure 1 – Retinal Capillary Hemangioblastoma (RCH) of the left eye located superior to the optic nerve head. Note the dilated afferent and efferent vessels emanating from the disc to the RCH.

Dilated fundus examination revealed a cup to disc ratio of 0.1 with sharp disc margins. The vitreous was clear. Notable on examination was an endophytic, pedunculated vascular lesion located superior to the optic nerve head with associated dilated, tortuous vessels without subretinal fluid or exudation (Figure 1). Fluorescein angiogram (FA) indicated early arteriolar filling of the lesion without significant leakage (Figure 2). Examination of the patient's 13-year-old brother revealed a similar appearing lesions in the periphery of the right eye (Figure 3).



Work Up and Course:

Considering the appearance of the lesion and the patient's family history of an involved mother with Renal Cell Carcinoma, the patient and her brother were diagnosed with Retinal Capillary Hemangioblastoma (RCH) which prompted concern for systemic malignancy as part of von Hippel-Lindau (VHL) disease. Screening evaluation reportedly indicated no systemic malignancy in the patient whereas her brother was found to have a pheochromocytoma.

In terms of the patient's RCH, there was concern for future development of exudation and vision loss. She underwent laser photocoagulation to the area surrounding the lesion which was ineffectual in inducing regression at 1 month follow-up (Figure 4). She subsequently underwent conjunctival cut-down with double freeze-thaw cryotherapy to the RCH which was successful in inducing regression of the lesion 1 month later without subsequent exudative reaction (Figure 5).

At final follow-up, the patient's vision remained stable with RCH regression and no evidence of systemic malignancy.

Discussion:

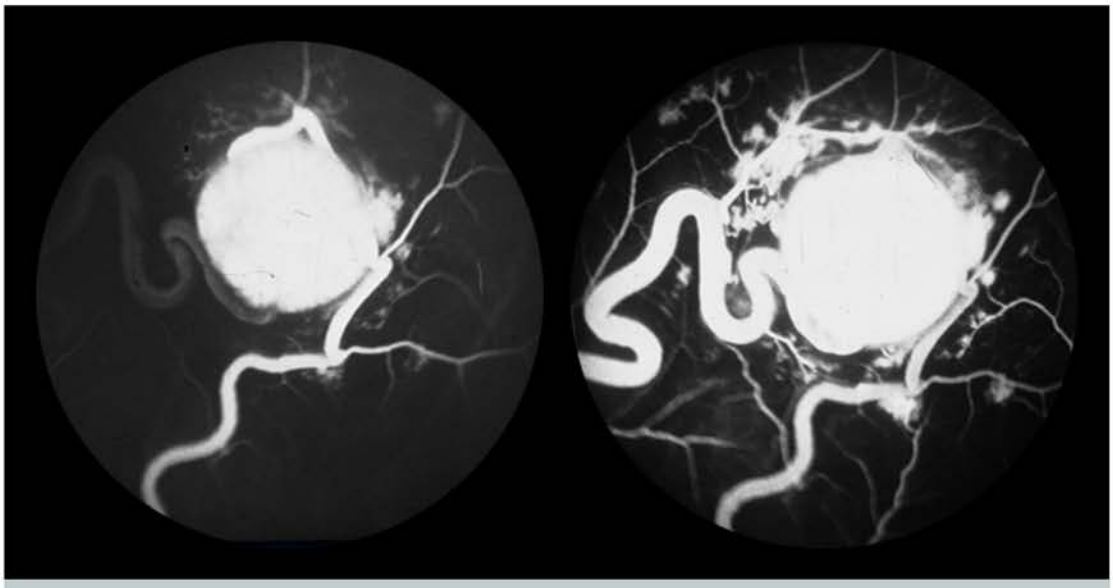


Figure 2 – Fluorescein angiography of the RCH exhibiting early filling without significant leakage.

Retinal Capillary Hemangioblastoma (RCH) is a vascular lesion that may occur in isolation or in the setting of von Hippel-Lindau (VHL) Disease. RCH is characterized by a globular vascularized lesion with dilated afferent and efferent blood vessels [1]. When smaller, RCH may be confused as a retinal macroaneurysm (RAMA) or telangiectasias associated with Coats' Disease. Although RCH may occur in isolation, it is the most commonly identified finding associated with von Hippel-Lindau (VHL) disease prompting concern for this serious condition [1,2].

VHL disease is an autosomal dominant condition with high penetrance characterized by benign and malignant tumors in the retina, brain, kidney, pancreas, and the adrenal gland [3]. It is due to mutation of the VHL tumor suppressor gene on chromosome 3 with an annual incidence of 1 case per 36,000 live births [3]. Similar to retinoblastoma, a two-hit hypothesis of VHL disease has been postulated with all individuals inheriting a germline mutation of the VHL gene which is present in all somatic cells [3]. Malignancy develops when a mutation in the second copy of the gene occurs at a later time in cells located in susceptible end organs. This suggests that advancing age increases the possibility of this occurring [1,3]. In the largest consecutive case series of RCH associated with VHL disease, there was no association between increasing age and the number, extent, or laterality of RCH lesions in the eye which suggests the formation of RCH in the retina may be determined early in life [1].

In terms of brain involvement, central nervous system hemangioblastomas occur in 60-80% of VHL disease patients and manifest due to tumor location and mass effect. Cerebellar hemangioblastomas may lead to increased intracranial pressure and ataxia. Asymptomatic lesions are benign [3]. In terms of renal involvement, there is a 70% lifetime risk for development of Renal Cell Carcinoma (RCC) with a mean age at diagnosis of approximately 40 years [3]. Pheochromocytoma arising from the adrenal gland can occur in approximately 5% of VHL disease patients with mean age at diagnosis of approximately 30 years [3]. Pancreatic cysts are commonly seen in VHL disease, but 5 to 10% of patients can develop pancreatic, non-secretory islet cell tumors [3]. Recommended screening for VHL disease involves a multidisciplinary approach and begins with ensuring potentially affected family members have also been included in screening and genetic counseling. To identify RCH, annual screening beginning in childhood with ophthalmologic examination recommended as early as age 1 year old. To identify CNS hemangioblastoma, MRI of the brain is recommended every 12 to 36 months beginning at 16 years old [3]. To identify renal and pancreatic malignancy,

Figure 3 – Small peripheral RCH in the right eye of the patient's 13-year-old brother.

MRI or ultrasound examination of the abdomen is recommended yearly starting at the age of 16 years [3]. For identification of pheochromocytoma, blood pressure monitoring and annual 24 hours urine catecholamine levels are recommended starting from the age of 5 years with adrenal imaging for age 8 years with earlier imaging n high-risk families [3].

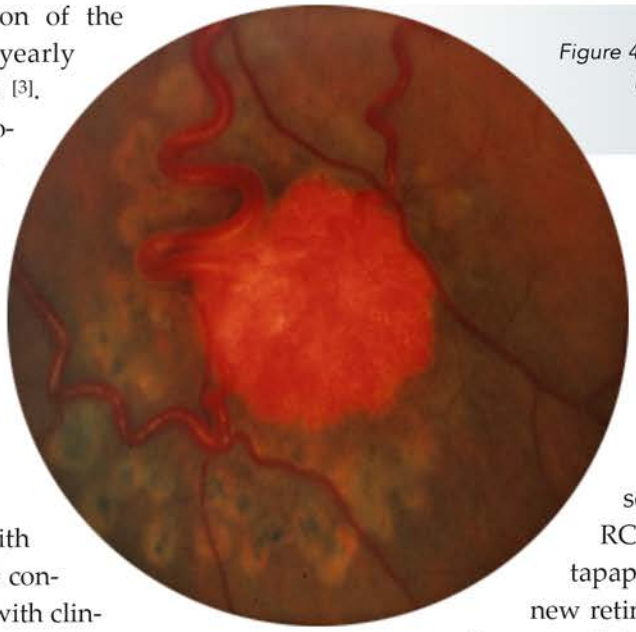


Figure 4 – Example of an RCH undergoing laser photocoagulation with failure of involution.

In regards to RCH associated with VHL disease, in the two largest consecutive-case series of patients with clinically definite VHL disease, 335 of 890 (38%) patients and 154 of 249 (62%) patients were found to have RCH [1,2]. In patients with VHL without evidence of RCH at initial examination, 27% developed new RCH lesions at a mean follow up of 8.2±4.0 years [2]. The mean age of RCH identification was 36.9 ±13.7 years and 33.3±13.5 years in the two largest series [1,2]. RCH can be unilateral (42.1%) or bilateral (57.9%) with approximately 85% of lesions manifesting in the periphery and 15% in the juxtapapillary area [1]. No cases of macular involvement of RCH were identified [1,2]. The average number of RCH lesions detected per eye were 2.5 ± 1.8 tumors per eye with approximately 25% of patients having greater than 1 quadrant of retinal involvement. There was no association between age, number of RCH lesions, or extent of RCH lesions identified [1].

Visual morbidity occurs with leakage and exudation from the lesion which is more common in juxtapapillary RCH. Rarely, these lesions bleed or even lead to the development of neovascular glaucoma through expression of vascular endothelial growth factor (VEGF). In terms of visual morbidity in the eyes involved by RCH, approximately 50% of eyes had BCVA of 20/20 or better, 20% had BCVA of 20/20 to 20/40, 10% had BCVA of 20/40 to 20/160, and 20% had BCVA of 20/160 or worse [1]. Of the 68 of 335 patients (20.3%) with "severe ocular involvement" defined as BCVA worse than 20/160, this was due to end-stage disease causing extensive exudative retinal detachment, phthisis bulbii, and anterior segment disorganization [1]. Attaining VA worse than 20/160 was associated with increasing age, juxtapapillary involvement (odds ratio 6.38), number of peripheral lesions > 5 (odds ratio 8.27) and > 1 quadrant of RCH involvement (odds ratio 26.58) [1]. In the longest longitudinal case series of VHL patients with RCH, eyes that developed new juxtapapillary RCH, developed RCH in new retinal locations, or experienced an increase > 3 in the number of peripheral RCH lesions were at greatest risk for vision loss.

Treatment for RCH aims to address potential vision loss by directly treating the lesions through ablative therapy such as laser photocoagulation, transpupillary thermotherapy (TTT), photodynamic therapy, and cryotherapy with size and location dictating choice of treatment modalities used [4]. Vitrectomy with ablative procedure as well as intravitreal anti-VEGF to treat RCH exudation has also been described [4,5]. In a series of patients from South Korea with RCH, small RCH (<0.5mm) were treated with laser photocoagulation, medium RCH (0.5 to 3.0 mm) were treated with TTT, and large RCH (> 3.0 mm) were treated with a combination of TTT and cryotherapy with RCH regression rates of 90%, 70%, and 67% respectively [4]. Treatment success was correlated with smaller RCH and peripheral RCH as compared to juxtapapillary RCH (p=0.01). Complications following treatment (described as increased exudation and exudative retinal detachment) occurred in 13.5% of eyes of which 1/5 were medium RCH and 4/5 were large RCH which prompted further treatment [4].

Conclusions:

Retinal Capillary Hemangioblastoma (RCH) may occur in isolation or as a part of von Hippel-Lindau (VHL) disease. VHL disease is an autosomal dominant condition following the two-hit hypothesis of germ-line inherited mutations characterized by tumors in the

retina (retinal capillary hemangioblastoma), brain (CNS hemangiomas), kidney (renal cysts and renal cell carcinoma), adrenal (pheochromocytoma), and pancreas (cysts and islet cell tumors). Screening for this condition requires a multidisciplinary approach and identification of all affected family members. RCH has been identified in 38 to 62% of patients with VHL disease. With longitudinal follow-up, 27% of patients may develop RCH that was not initially detected. Approximately 60% of cases of RCH are bilateral with an average of 2.5 ± 1.8 tumors per eye with typically only 1 quadrant involved in 75% of patients. Visual morbidity from RCH typically occurs with leakage and exudation with worse prognosis associated with increasing age, juxtapapillary involvement of the RCH, increased number of peripheral RCH lesions, and increased extent of quadrants involved. Treatment for RCH involves ablating the lesion. Smaller and more peripheral RCH lesions are more amenable to successful treatment.

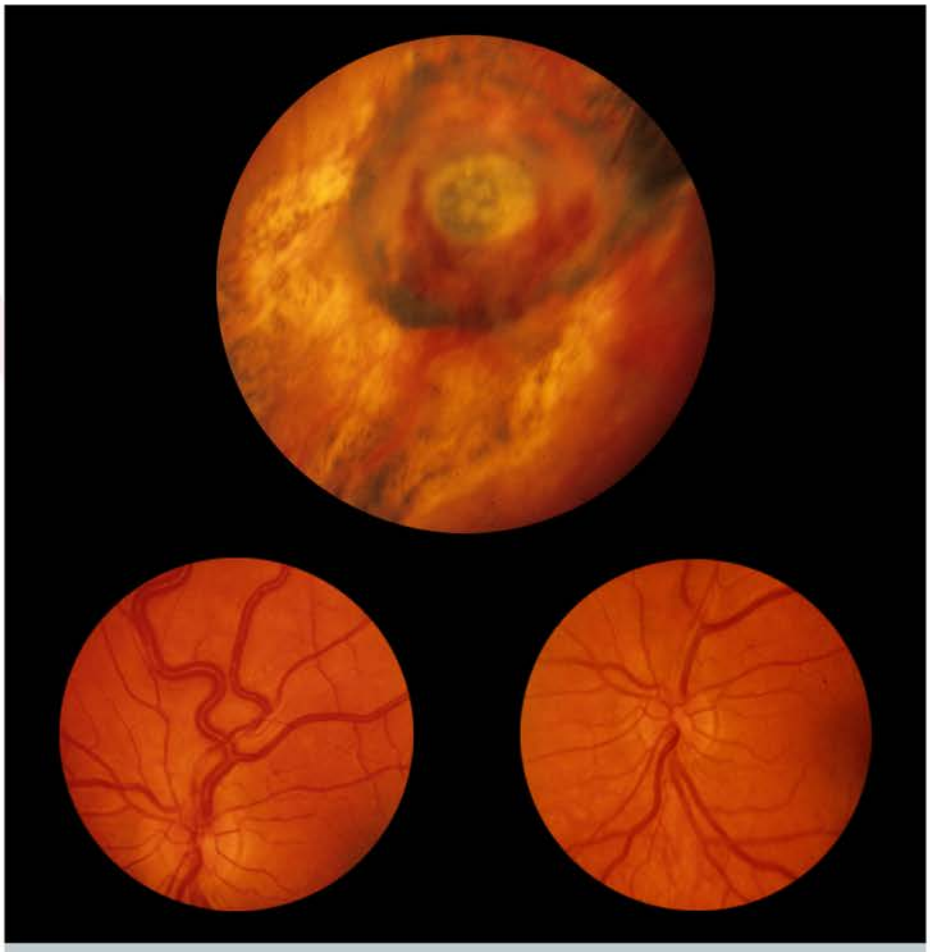


Figure 5 – Patient's RCH after treatment with cryotherapy with successful involution. Note the resolution of the vascular tortuosity and dilation after successful treatment.

References:

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