Case series of retinal capillary hemangioma in patients with and without von hippel lindau disease

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Background: To report six cases of retinal capillary hemangioma (RCH) in patients with and without Von Hippel Lindau (VHL) disease to observe the presenting age, clinical features, treatment modalities and visual outcome of each patient.
Methods: Case series
Results: All patients showed unilateral involvement. The presenting symptoms for both groups were mainly chronic generalised painless blurring of vision and central scotoma. Among three of VHL patients, fundus examinations revealed one patient had solitary retinal angioma with exudates and the other two had multiple retinal angioma with various sizes and locations. Two of the patients had focal laser done to each eye and one patient had both focal laser and intravitreal ranibizumab injection. In three other patients without VHL (sporadic), fundus examinations revealed multiple peripheral retinal angioma with pre-retinal haemorrhage in one patient and juxtapapillary RCH in two patients. The first patient developed vitreous haemorrhage and underwent vitrectomy twice and endolaser therapy. The other two patients with juxtapapillary RCH received intravitreal ranibizumab in each eye and one of them had Verteporfin photodynamic therapy.
Conclusion: Age at presentation of sporadic tumors can be as early as in teenagehood. From the case series, juxtapapillary RCH occurs more in sporadic cases with higher risk to develop vision threatening complication. Current treatment is able to achieve vision stability but not a complete regression of the retinal lesion hence the eyes are always at risk.
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Introduction

The Von Hippel Lindau (VHL) is a rare disease first reported in the twentieth century. It is an autosomal dominant disorder that implies a genetic alteration resulting in the loss of the tumor suppressor function of the VHL gene[1] located in chromosome 3 (3p25.3).

In 1904, Eugene von Hippel, a German ophthalmologist, described some cases of retinal angiomatosis. After some 20 years, Lindau, a Swedish pathologist, established the relationship between the

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cerebellar and retinal lesions in 1926. In 1964, Melmon and Rosen reported cases of von Hippel disease and Lindau disease with overlapping ophthalmic, central nervous system, and visceral manifestations, establishing the clinical spectrum and diagnostic criteria of "von Hippel-Lindau" disease (VHL)[2]. The incidence of the disease is approximately 1/36,000 in the general population, but with a high penetrance in the affected families, reaching 90% at 65 years of age[3,4], which justifies the high risk of developing its related diseases in the individuals that carry the mutation.

The main manifestations of VHL are hemangioblastomas of the central nervous system and retina, renal carcinomas and cysts, bilateral pheochromocytomas, cystic and solid tumors of the pancreas, cystadenomas of the epididymis, and endolymphatic sac tumors

Retinal capillary hemangioma (RCH) is a benign vascular tumor of the retina that can occur sporadically or in association with von Hippel-Lindau (VHL) disease[5]. When it is related to VHL disease, RCH is the common feature of VHL disease and are often the first manifestation of the disease (up to 43% of gene carriers)[6].

The purpose of this report is to present six cases of RCH in patients with and without VHL to observe the presenting age, clinical characteristics (including tumor growth type and location), treatment modalities and visual outcome in each of the treatment given to patients.

Case Presentation

Six patients with retinal capillary hemangioma with VHL and without VHL disease were seen at Ophthalmology Clinic, Hospital Selayang. Background ocular history, associated symptoms and thorough eye examinations including fundus photo, OCT and FFA were taken and performed in each individual patient.

Case 1

A 24-year-old gentleman with a family history of VHL presented with progressive worsening blurring of vision of the left eye for 2 months. The LE BCVA was 6/9. His right eye was normal. Dilated fundus examination showed a solitary retinal angioma with surrounding exudates at the peripheral superotemporal region (Figure 1). LE focal laser to the feeder artery was given and the lesion seemed stable as the retinal angioma contracted with surrounding fibrosis during the last clinic visit after a year of treatment (Figure 2). Final LE BCVA for the patient was 6/9. The patient was further subjected to whole body MRI screening for concurrent existing of other hemangioma or visceral lesions. His MRI was revealed to be normal.

Case 2

A 38-year-old gentleman with a family history of VHL with RCH initially presented in 2018 for right eye blurring of vision for 2 months. His left eye was blind since childhood. The RE BCVA was 3/60 ph 6/60. Right eye fundus examination showed presence of multiple retinal angioma, the largest being at the temporal quadrant and few at the superior and inferior retina. RE FFA showed leakage near the lesions (Figure 3) and OCT showed presence of subretinal fluid on macula. Hence the eye was treated with two sessions of intravitreal Ranibizumab and focal laser. During subsequent follow up, the lesion at the temporal quadrant had focal detachment

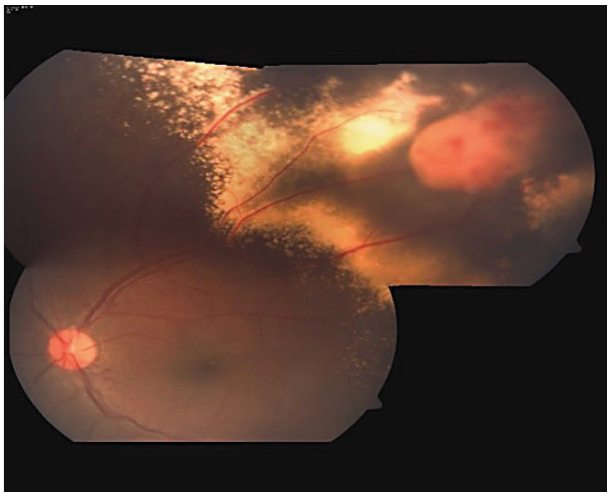

Figure 1 Montage fundus photography showing left solitary RCH over superotemporal retina with surrounding exudates

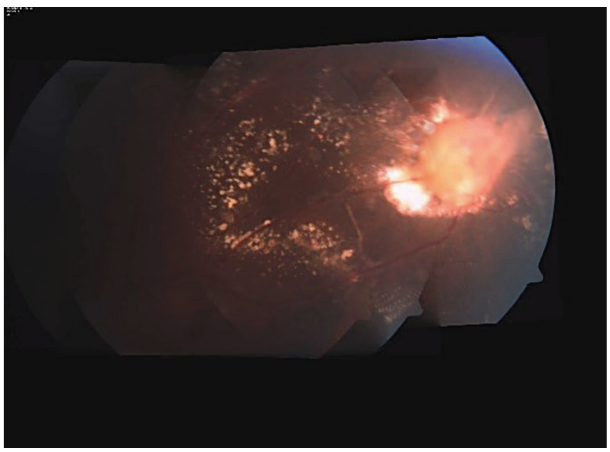

Figure 2 Fundus photography showing contracting tumor post focal laser

with persistent small angioma at inferior quadrant. Barricade laser was done at the detachment area and another focal laser given to the area of the smaller tumor. A month later revealed a dilated, tortuous feeding vessel located temporally to the angioma. Laser ablation was given to the vessel and post laser treatment resulted in a sclerosed feeder vessel but not completely obliterated nevertheless the lesion seemed stable. The final BCVA of the RE was 6/36 ph 6/18.

Case 3

A 38-year-old man with VHL disease, pheochromocytoma and post nephrectomy complained of right eye central scotoma for 2 weeks. The visual acuity in the right eye was 6/36. The left eye was normal. Funduscopic examination of the right eye revealed 2 retinal angiomas superotemporally with surrounding oedema and exudates. RE focal laser was performed on the lesions. Subsequent follow up showed contraction of the smaller angioma but the bigger angioma did not

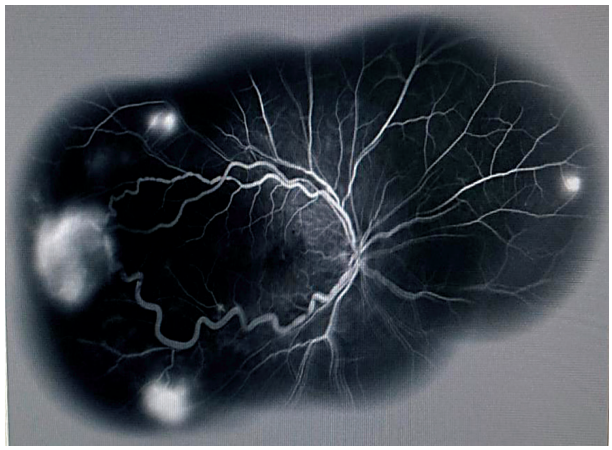

Figure 3 Right eye montage FFA showing multiple lesions with leakage near the lesions: largest at temporal and 1 smaller lesion each at superior, nasal and inferior retina

show any improvement and was seen projecting into the vitreous. The lesion was observed in view of high risk of bleeding. Over the next 2 years, the lesion remains stable and contracted (Figure 4&5). Repeated FFA showed no leakage from the angioma and was treated conservatively. The visual acuity of 6/36 remained stable in the right eye till the date of writing the case.

Case 4

A 13-year-old boy complained of left eye squint with reduced vision for 2 months. The visual acuity in the left eye was 6/60. The right eye was normal. Funduscopic examination revealed an abnormal peripapillary vascularisation with fibrosis nasally (Figure 6). He was treated with LE intravitreal Ranibizumab.

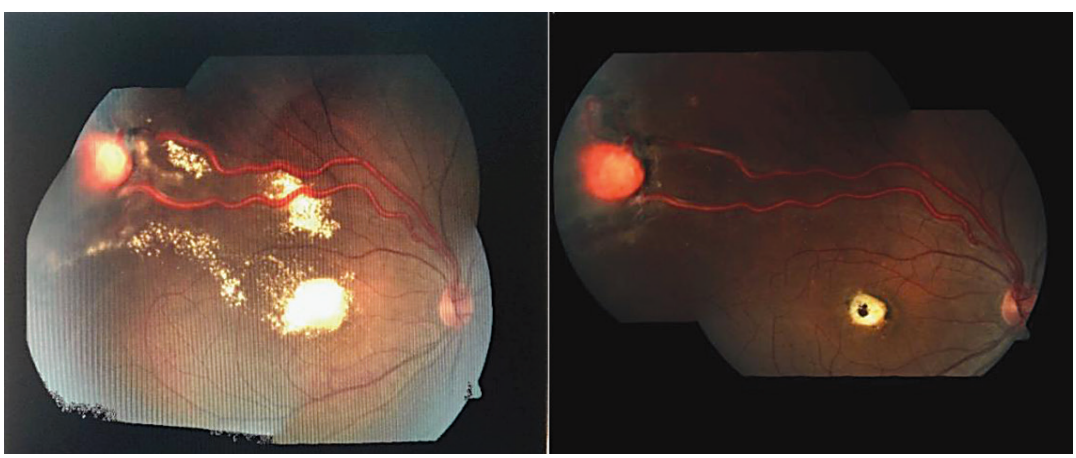

Figure 4 &5 Right eye serial fundus photography showing contraction of retinal hemangioma and resolution of macula exudates

Post injection, the patient developed a localised TRD at angioma. LE vitrectomy and endolaser was done. A year later, the contracting angioma at the disc caused retinal traction at the surrounding area including the macula (Figure 7). No active intervention was done. His final visual acuity was 6/60.

Case 5

A 37-year-old man presented with the complaint of progressive left eye blurring of vision for 1 month. The visual acuity of the LE was 6/18. Dilated fundus examination showed a reddish subretinal lesion at the juxtapapillary region with surrounding exudates and SRF

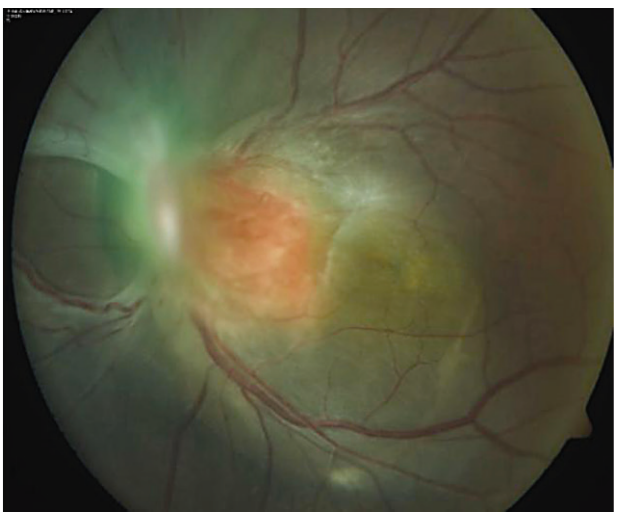

Figure 6 Left eye fundus photography showing peripapillary abnormal vascularization with nasal fibrosis

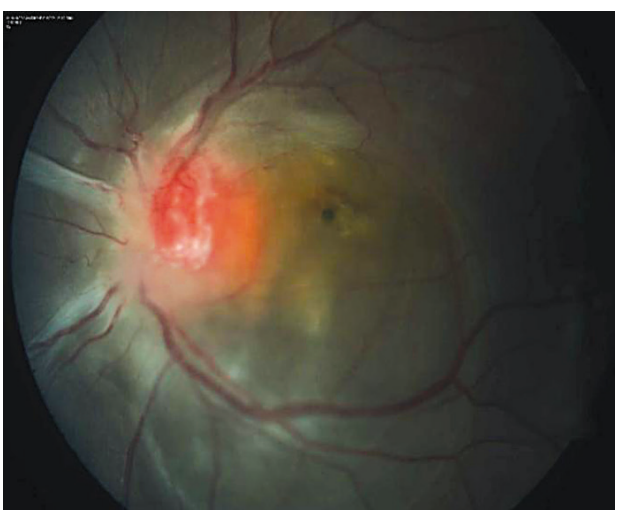

Figure 7 Left eye fundus photography 1 year post treatment

(Figure 8). OCT showed subretinal and intraretinal fluid near the OD and FFA resulted in increased hyperfluorescence juxtapapillary (Figure 9). Patient was treated with intravitreal Ranibizumab. Subsequent follow up at 3 months post intravitreal Ranibizumab, his visual acuity dropped to CF 3 ft and more subretinal exudates were seen. Repeated FFA showed a hyperfluorescent lesion with increasing size and intensity, well defined margin with no feeder vessel. Patient was then treated with LE full fluence PDT. Post PDT, patient had persistent macular oedema. His best last recorded final VA was 6/60. He then migrated to another country and had his eye follow up over there.

Case 6

A 62-year-old man with chronic myeloid leukaemia and LE pseudophakia presented with generalised LE blurring

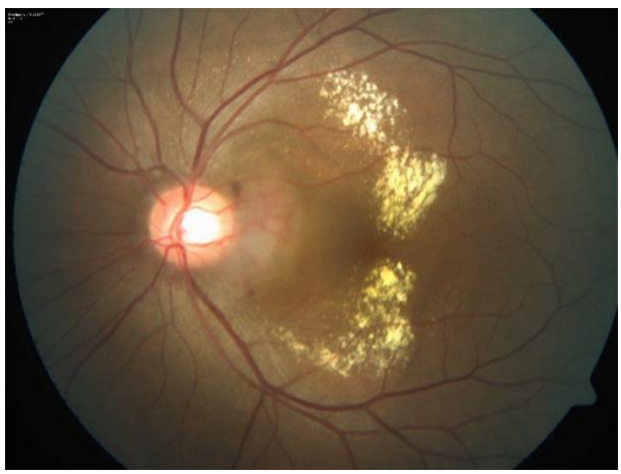

Figure 8 Left eye fundus photography showing subretinal reddish lesion at juxtapapillary with surrounding exudates and SRF

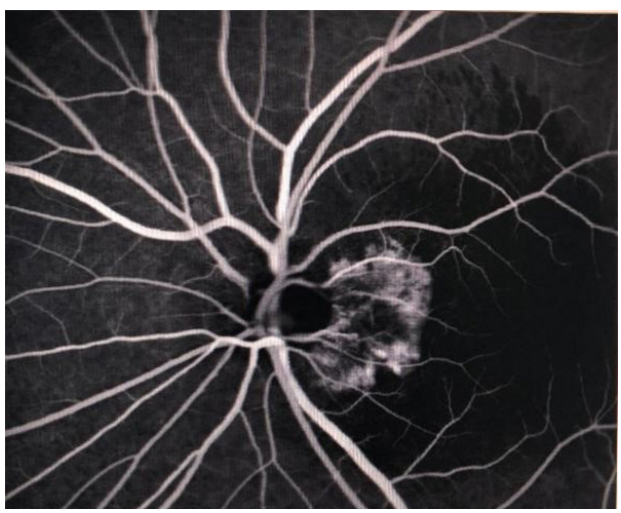

Figure 9 Left eye FFA showing peripapillary hyperfluorescent lesion

of vision for 3 months. The visual acuity of the LE was HM. The RE was normal. Fundus examination revealed LE pre-retinal haemorrhage at the superior quadrant and 3 vascularized lesions, 1DD each at peripheral temporal quadrant. Subsequently, the patient developed vitreous hemorrhage and underwent LE PPV/ endolaser. FFA postoperatively noted LE chronic macula edema and capillary fall out area seen at nasally and inferiorly with no feeder vessels seen. LE PRP laser was performed to the nonperfused retina. Patient had LE recurrent VH 1 year later and underwent another LE PPV with endolaser treatment. Post operatively, the LE retinal lesion reduced in size with surrounding fibrosis and a final VA of 6/18.

Results

A total of six cases of RCH (three patients with VHL and three without VHL disease) were collected to observe the presenting age, clinical features and treatment prescribed. All the patients were male and had unilateral involvement. Presenting symptoms for both groups were mainly chronic generalised painless blurring of vision with central scotoma.

For VHL patients, the age ranged from 24 to 38 years old. The presenting best-corrected visual acuity (BCVA) ranged from 6/9 to 3/60. Fundus examinations revealed 1 patient had solitary retinal angioma with exudates and the other 2 had multiple retinal angioma with various sizes and locations. Two of them had focal laser done to each eye and the third patient was given focal laser and intravitreal ranibizumab.

Meanwhile, for cases without VHL, the age ranged from 13 to 62 years old. The presenting BCVA ranged from 6/18 to HM. Dilated funduscopic examinations revealed multiple peripheral retinal angioma with pre-retinal haemorrhage in one patient and juxtapapillary RCH in the other two patients. The first patient developed vitreous haemorrhage and underwent vitrectomy twice and endolaser therapy. The remaining two patients with juxtapapillary RCH, the first one was treated with intravitreal Ranibizumab and Verteporfin photodynamic therapy whilst the other was treated with intravitreal Ranibizumab only. The latter developed localised TRD at angioma and underwent vitrectomy and endolaser.

Discussion

Retinal capillary hemangioma (RCH) are benign vascular tumors that can appear sporadically or are associated with VHL disease. Although RCH usually manifests as a solitary unilateral tumor, when associated with VHL disease, up to half the cases may have multifocal or bilateral involvement[7]. In the current case series, all the patients including in association with VHL show unilateral involvement and 2 out of 3 patients with VHL have multifocal lesions (case 2 and 3).

In bilateral cases, they generally exhibit symptoms and produce severe visual impairment in 5–8% of patients. The growth of RCH is usually slow and endophytic, with peripheral retinal location although they could also be juxtapapillary.

Arun D Singh et al in 2002 found that approximately half of the patients with solitary RCH are expected

to have underlying VHL disease and detailed clinical evaluation in patients with solitary RCH is recommended using standard screening protocols[7]. In this current study, one of the RCH patients with VHL presented with a solitary lesion underwent screening protocols as well (case 1). Juxtapapillary RCH tends to occur more commonly in sporadic cases, as in this series, 2 out of 3 patients without VHL presented with has juxtapapillary RCH (case 4 and 5).

Epidemiologically, in one of the case series, McCabe CM et al in 2000 found that the age at diagnosis of hemangioma was younger for patients with VHL disease, who were first seen at a mean age of 20 years, compared with those without VHL, who were first seen at a mean age of 44 years[6]. In contrast to previous study, the youngest age at presentation was found in sporadic cases in this case series, as early as at the age of 13 years old (case 4).

The diagnosis of VHL is based on the assessment of three criteria: retinal or CNS hemangioma, visceral lesions, and family history. If the patient has a family history of VHL disease, only one hemangioma or visceral lesion confirms the disease. In cases with no family history of VHL disease, the presence of two or more hemangiomas, or a hemangioma and a visceral lesion are needed for the diagnosis[1]. Even though the clinical diagnosis can be based solely on the presence of typical lesions, genetic testing to establish and/or confirm the definite diagnosis is indicated for all patients with suspected VHL disease[8]. In the current study, two of the diagnosed VHL patients have positive family history (case 1 and case 2) whereby another one patient with VHL was diagnosed due to presence of RCH and pheochromocytoma (case 3).

Juxtapapillary retinal capillary hemangioma (JRCH) are vascular hamartomas that occur on the optic nerve head or within the juxtapapillary region. It is usually misdiagnosed with papillitis, papilledema, choroidal neovascularization or choroiditis[9]. JRCH is almost always related to progressive loss of vision secondary to macular exudates or serous retinal detachment . It occurs most commonly on the temporal side of the disc, and therefore adjacent serous retinal detachment tends to affect the macular region, resulting in loss of vision. Both complications could be seen from this case series as one of the patients with JRCH had extensive macular exudates (case 5) and complicated with serous retinal detachment resulting in poor visual outcome.

The treatment of RCH depends on location, size and clinical expressions. RCH is most frequently managed by observation, laser photocoagulation, and cryotherapy. Careful observation in a reliable patient is recommended if the RCH is very small (up to 500 micrometer), not associated with exudation or subretinal fluid, and is not visually threatening because of a nasal location. All of our patients had some form of intervention, none were purely observed. Photocoagulation is currently used to treat smaller RCH located in the posterior retina in eyes with clear media. Laser photocoagulation, applied over many sessions, is most effective in tumors that are 1.5 mm or smaller but can be considered for RCH that are up to 4.5 mm. The technique of photocoagulation includes

placement of photocoagulation marks, delimiting the lesion, on the surface of the lesion, and on the feeding artery[7]. In a study by Blodi CF et al in 1990 who compared different techniques of direct and feeder vessel photocoagulation, both were found to be safe and effective, but the feeder vessel technique required a greater number of treatment sessions[10]. The resolution of subretinal fluid, tumor shrinkage with narrowing of vessels, or change of color of RCH from red to pale pink is indicative of an adequate response to treatment, and complete obliteration of the RCH is not necessary to achieve clinical resolution. In our case series, focal laser photocoagulation was performed in all 3 of the RCH with VHL patients (case 1, 2 and 3). It is due to their peripheral location, small to medium sized RCH and in a clear media.

Cryotherapy is preferable to photocoagulation when the RCH is located anteriorly with a significant amount of subretinal fluid and the RCH is more than 3.0 mm in diameter[7]. However, none of our patients are suitable for the cryotherapy treatment.

Vitreoretinal surgical intervention is usually required for larger RCHs complicated by rhegmatogenous or tractional retinal detachment[11]. During vitrectomy, direct diathermy and endolaser can also be performed. From our case series, 1 of the patient in RCH group without VHL required vitrectomy and endolaser as he developed complication of vitreous haemorrhage.(case 6)

Rarely, enucleation is performed for management of a blind painful eye because of end-stage complications[7].

Intravitreal injection of anti-VEGF has been proposed but in isolation as it does not appear to be efficient even though it could diminish the progression of small lesions and retinal edema[12, 13]. One of the patients with RCH and VHL was supplemented with intravitreal Ranibizumab twice as he had multiple retinal angioma with subretinal fluid that threatened the macula (case 2).

In general, juxtapapillary RCHs (JRCHs) are treated if they are progressive or if they affect visual acuity (VA)[7]. There is no single effective treatment in treating JRCH to date. If the JRCH is not associated with SRF, exudation, and vision-threatening, careful observation is recommended. Laser photocoagulation is effectively used to treat small RCH (up to 1.5 mm) in the posterior retina but carries additional risk for JRCH due to the proximity to the optic nerve[14]. The treatment of JRCH usually requires multiple and intense burns and damages the nerve fiber layer, causing a permanent scotoma and irreversible decline of the VA. However, repeated applications of low to moderate-intensity photocoagulation to the angioma can result in stabilization or improvement in visual acuity[6].

Radiotherapy, cryotherapy, and transpupillary thermotherapy are commonly used to treat large JRCHs, located in the peripheral retina and away from the optic nerve. Vitreoretinal surgery can also serve as an alternative when glial proliferation leads to epiretinal membrane development or tractional retinal detachment. As can be seen in case 4, the patient had LE intravitreal Ranibizumab complicated with localised TRD at angioma post injection and underwent LE vitrectomy and endolaser.

Anti-VEGF therapy has been reported to reduce vascular permeability by altering the

balance of vasoactive cytokines like nitric oxide and endothelin-1 or by directly altering endothelial tight junction proteins[15]. It is postulated that excessive accumulation of hypoxia-induced factor in the neoplastic stromal cells of RCH leads to the production of other angiogenic factors that are able to maintain and promote the growth of primary hemangiomas[11].

E Chelala et al in 2013 reported a case of a JRCH patient with von Hippel–Lindau with well-preserved visual acuity (VA) and visual field (VF) received a single injection of intravitreal ranibizumab (IVR). Six months after IVR injection, the JRCH showed reduced vascularisation, fibrosis, and mild shrinkage, and VA and VF remained unchanged. Ranibizumab likely inhibited VEGF in and around the tumor and also suppressed permeability via the blockage of VEGF. Also, IVR seems to have the advantage of a decreased potential for retinal damage compared with other treatments for JRCH[13].

PDT is an alternative method to treat JRCH as it enables a selective vascular occlusion and appears to be less damaging to adjacent neural structures[16]. PDT might cause fibrosis and involution of the small JRCHs. In the case of large tumors, verteporfin may only be activated on the surface of the tumor, and the reactive oxygen species may not allow closure of the deeper tumor vessels[17]. Although PDT has been reported to be effective in treating macular edema and SRF in JRCH[18], it has some complications, such as retinal vessel occlusion, optic neuropathy, tractional retinal detachment, epiretinal membrane, and massive subretinal hemorrhage[19].

According to Schmidt-Erfurth et al, 2002, they conducted a study on 5 patients with papillary RCH treated with PDT and found out that tumor regression with resolution of macular exudate and serous retinal detachment was obtained in all eyes but PDT did not helps in improvement of vision and yet worsening of vision in 3 patients. A decline in VA of 1, 3, and 10 lines, respectively, were documented in three patients[17].

Tong et al 2018 conducted study in JRCH patients treated with two sessions of full-fluence PDT at an interval of 3 months. After 2 years of follow-up, they found that the VA improved, the hemangioma significantly reduced in size, the SRF reabsorbed, and exudation and macular edema regressed[20].

Recent reports of combined therapy with anti-VEGF and PDT have shown promising results in these lesions. A few study conducted including Ziemssen et al in 2007 reported a case of JRCH successfully treated with a single combination of intravitreal bevacizumab and PDT. The patient had marked regression of the hemangioma, an increase in VA, regression of the scotoma on VF testing, and macular drying that persisted after 1 year[21].

A study by Mennel et al in 2010 found that the combination of intravitreal anti VEGF and PDT proved to be an effective strategy for the treatment of retinal juxtapapillary capillary haemangioma without side-effects. A patient was given two sessions of PDT (sparing the part of the haemangioma located within the optic disc) and five injections of bevacizumab were applied in a period of 5 months. One year after the last injection, there was an improvement in visual acuity, resolution

of all lipid exudates at the posterior pole and restoration of normal central macular architecture. Visual field testing and angiography did not show any treatment-related vaso-occlusive side-effects[22].

By combining anti-VEGF with reduced fluence PDT, the outline of the primary angioma can be better delineated and may thus reduce the energy and the treatment area, thereby minimizing the damage to the neurological tissues.

In contrast with the current study, both patients (case 4 and 5) with JRCH were given intravitreal ranibizumab but the outcome differed. In case 4, the patient developed tractional retinal detachment shortly after the injection requiring vitrectomy and endolaser. As in case 5, due to poor vision post injection caused by more subretinal exudates, the patient was treated with full fluence PDT. Unfortunately, post PDT, the patient still had persistent macular oedema but was able to gain better final visual acuity which was 6/60. None of the complications related to PDT was observed in this patient and none of our patients received combination treatment at first sitting.

Conclusion

Retinal capillary hemangioma (RCH) with or without VHL are all unilateral involvement but age at presentation of sporadic tumors can be as early as in teenage. From the case series, juxtapapillary RCH occurs more in sporadic cases with higher risk to develop vision threatening complication. Current treatment is able to achieve vision stability but not a complete regression of the retinal lesion hence the patient's vision is always at risk.

Disclosures

Human subject: consent was obtained by all participants in this study.

Conflicts of interest: all of authors have declared that no financial support was received from any organization for the submitted work, no financial relationship at present with any organization that might have an interest in the submitted work and there are no other relationship or activities that could appear to have influenced the submitted work.

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