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Case Report

Persistent exudative retinal detachment after photodynamic therapy and intravitreal bevacizumab injection for multiple retinal capillary hemangiomas in a patient with von Hippel–Lindau disease

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Abstract

Photodynamic therapy (PDT) has been used in treating peripheral retinal capillary hemangioma (RCH) with satisfactory results. We report a rare case of von Hippel-Lindau (VHL) disease with three large peripheral RCHs, treated with PDT and intravitreal bevacizumab injection (IVB), who developed persistent bullous exudative retinal detachment (RD) despite significant tumor regression. The patient is a sporadic case of VHL disease, with a *de novo* nonsense mutation in codon 161 with C → T transition at nucleotide position 694 of the *VHL* gene. Multiple RCHs were noted in both eyes. Four small RCHs were found in the left eye and were treated with laser photocoagulation. Three large RCHs in the peripheral retina of the right eye were complicated with cystoid macular edema and subretinal fluid accumulation. The RCHs were treated with PDT combined with IVB, and bullous exudative RD developed on the second day after treatment. Three months after PDT, the tumors had regressed significantly, but exudative RD persisted, despite multiple IVB and intravitreal triamcinolone acetonide injection (IVTA). External drainage with sclera buckling, IVB, and IVTA were performed, and the retina attached after surgical intervention. The application of PDT in the treatment of RCHs and its possible complications are discussed.

Keywords: exudative retinal detachment; photodynamic therapy; retinal capillary hemangioma; von Hippel–Lindau

1. Introduction

Retinal capillary hemangioma (RCH) is a benign vascular tumor which may occur sporadically or as a manifestation of von Hippel-Lindau (VHL) disease.[1] The visual prognosis is usually unfavorable, due to exudation from the tumor, causing intraretinal edema or exudative retinal detachment (RD). According to its location, RCH can be classified as a peripheral or a juxtapapillary type. Current treatment modalities for RCH include laser photocoagulation, cryotherapy, radiotherapy, traspupillary thermotherapy, and vitreoretinal surgery.[1,2] Laser photocoagulation and cryotherapy are the two major conventional therapies, and are effective as the sole method of treatment in controlling 74% and 72% of peripheral tumors, respectively.[2] However, larger tumors need multiple sessions of therapy, which may cause extensive exudative RD. In recent years, photodynamic therapy (PDT) has been used in treating large peripheral RCH with satisfactory results.[3] Most tumors regress with decreased exudation. We report a rare case of VHL disease, with three large peripheral RCHs treated with PDT and intravitreal bevacizumab injection (IVB), who developed persistent bullous exudative RD despite significant tumor regression.

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2. Case report

A 23-year-old Taiwanese female had blurred vision in the right eye for 5 months. She had a past history of multiple intramedullary hemangiomas and had received two neurosurgeries to excise tumors at 14 years old and 22 years old. Reviewing the medical history of her family members, there was no known history of VHL disease or associated tumors. Genotyping of the *VHL* gene was performed after obtaining informed consent from the patient and her family members. Genomic DNA was extracted from peripheral venous blood samples. The three exons of the *VHL* gene were amplified by polymerase chain reaction (PCR) and sent to the National Yang-Ming University Genome Research Center for genotyping.

The presenting best-corrected visual acuity (BCVA) was 3/60 in the right eye and 6/5 in the left eye. There were no cells or flare in the anterior segment. Fundus examination revealed three large peripheral RCHs in the right eye, with prominent feeding arteries and tortuous dilated draining veins, complicated with subretinal fluid accumulation (Fig. 1A). Optical coherent tomography (OCT) showed marked cystoid macular edema and subretinal fluid accumulation at the macula (Fig. 2A). Fluorescein angiography of the tumors showed early hyperfluorescence with profound late leakage (Fig. 3). There were also four small peripheral RCHs in the left eye (Fig. 4A and B). The tumors in the left eye were treated with focal photocoagulation and regressed to gliotic nodules (Fig. 4C).

After obtaining informed consent, IVB 2.5 mg was administered to the right eye. Subretinal fluid was decreased

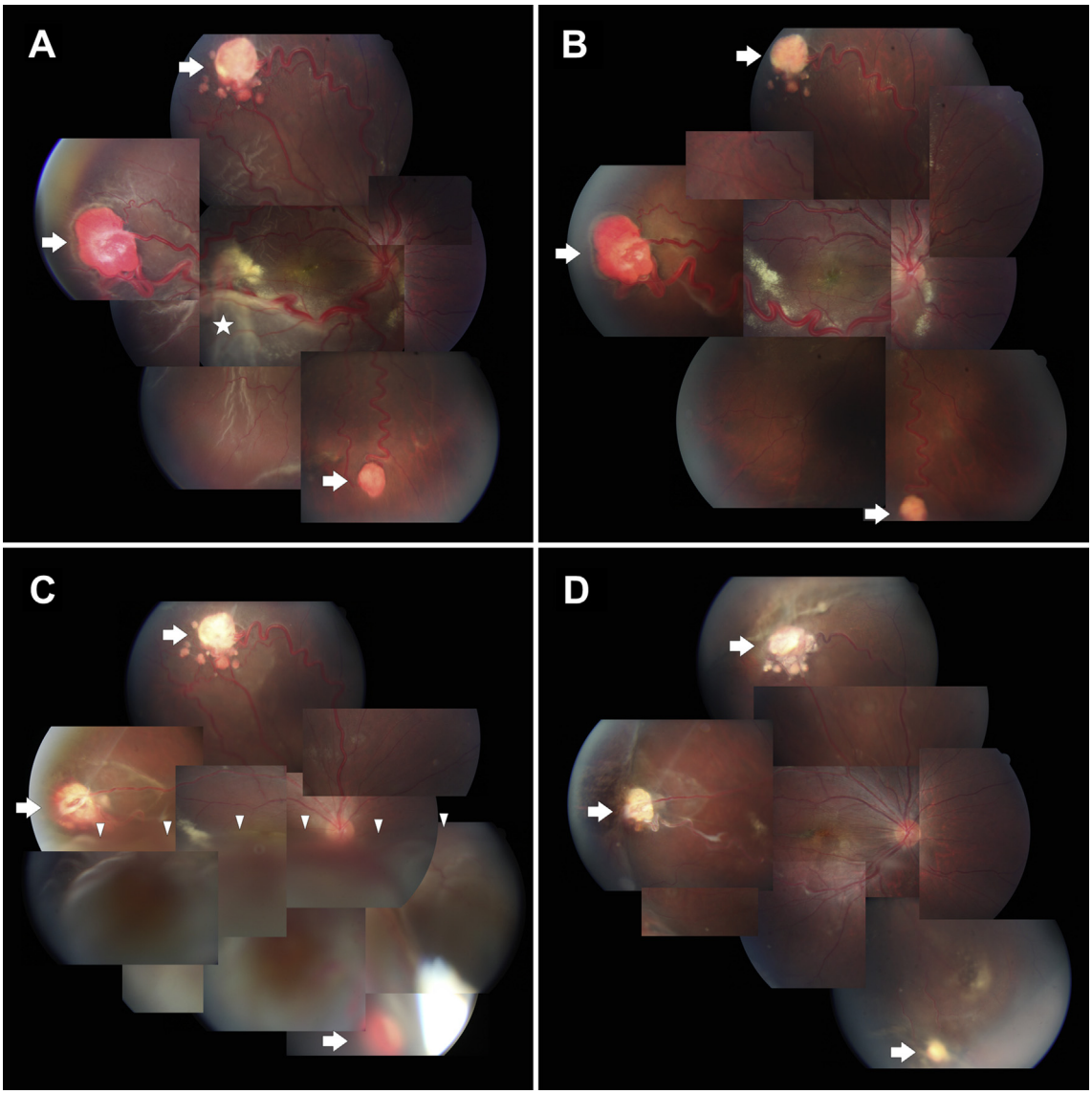

Fig. 1. (A) Three large retinal capillary hemangiomas in the peripheral retina in the right eye (arrows) with subretinal fluid accumulation (star) and lipid exudate at the macula; (B) decreased subretinal fluid and lipid exudate were noted at 1 week after 2.5 mg intravitreal bevacizumab injection; (C) 3 months after photodynamic therapy and intravitreal bevacizumab injection, the tumors showed significant regression (arrows). However, massive exudation with bullous retinal detachment persisted (below arrowheads) despite oral prednisolone and intravitreal injection of bevacizumab and triamcinolone acetonide; and (D) gliotic tumors (arrows) with resolved subretinal fluid at 3 months after surgical intervention.

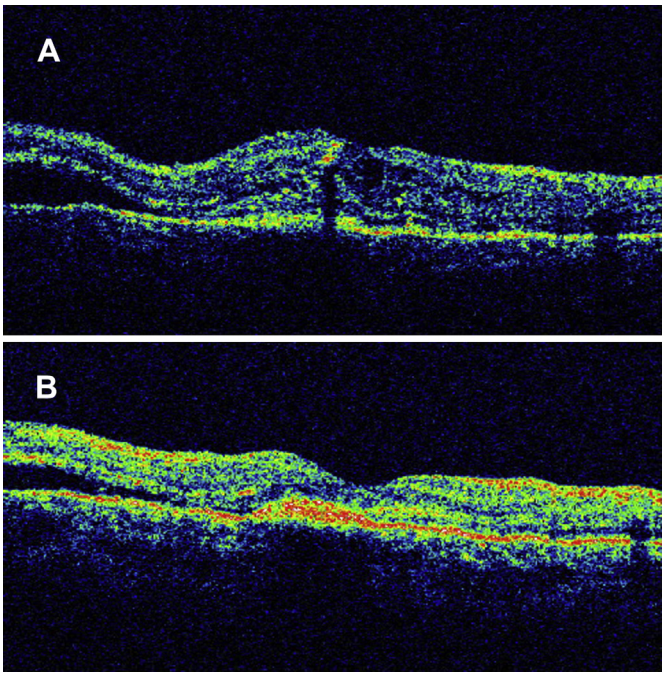

Fig. 2. Optical coherence tomography of the right eye macula showed (A) marked cystoid macular edema and subretinal fluid accumulation at presentation; and (B) significant decrease in the exudation at 1 week after intravitreal bevacizumab injection.

markedly with significant regression of cystoid macular edema at 1 week after injection (Figs. 1B and 2B), and BCVA improved to 5/60. One month later, a session of verteporfin PDT according to the standard protocol for age-related macular degeneration, combined with IVB 2.5 mg, was performed to the right eye. PDT was performed using 6 mg/m^2 body surface area of intravenous verteporfin infused over 10 minutes. Fifteen minutes after the start of infusion, a laser at wavelength 689 nm was delivered at 50 J/cm^2, with an intensity of 600 mW/cm^2 over 83 seconds, using spot sizes of 5000 μm, 5000 μm, and 2000 μm directly to the three tumors, respectively.

Bullous exudative RD developed during the second day, and BCVA dropped to 3/60. Oral prednisolone 1 mg/kg/day and two further IVB, one of which was combined with intravitreal triamcinolone acetonide injection (IVTA) 2 mg, were performed at 1 month intervals for persistent exudative RD. Three months after PDT, the tumors had regressed significantly, but exudative RD persisted (Fig. 1C). External drainage with scleral buckling, IVB, and IVTA were thus performed. The retina was attached after surgical intervention (Fig. 1D), and BCVA improved to 6/60.

Genotyping of the *VHL* gene of the patient found a C → T transition at nucleotide position 694, which resulted in a nonsense mutation of Arg161stop in exon 3 (Fig. 5A). However, her parents and three brothers were devoid of this mutation or any other mutations in the *VHL* gene (Fig. 5B).

3. Discussion

VHL disease is a multisystem disorder which may be associated with RCH, central nervous system hemangioma,

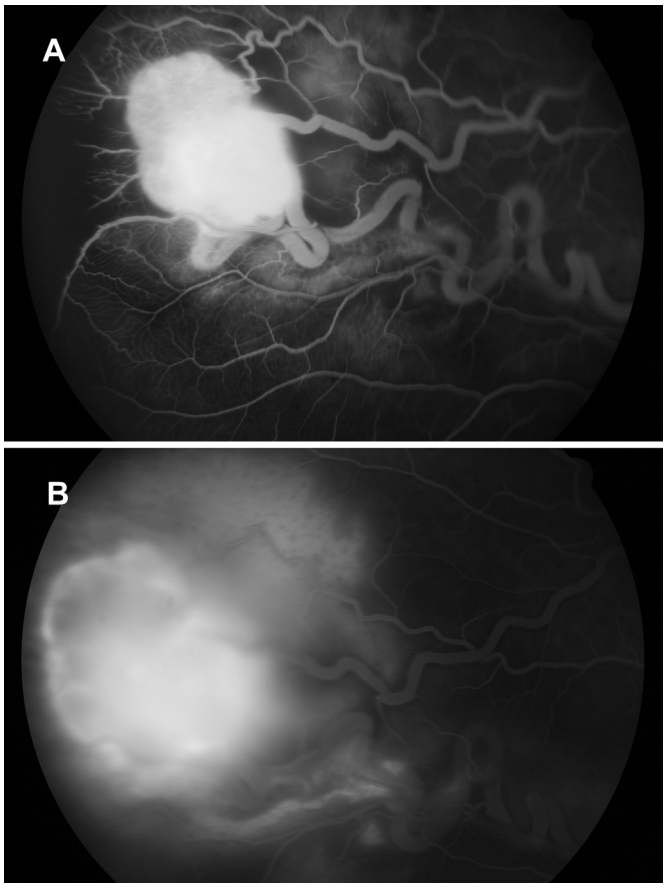

Fig. 3. Fluorescein angiography of the peripheral retinal capillary hemangioma (RCH) at temporal retina of the right eye showed (A) early hyperfluorescence; and (B) marked late phase leakage.

and other visceral tumors, such as pheochromocytoma and renal cell carcinoma.[1,4] The disease is diagnosed with a positive family history of VHL disease with one associated tumor. In the absence of a definite family history, at least two RCHs or central nervous system hemangiomas, or one hemangioma plus one visceral tumor, establish the diagnosis.[4] It is an autosomal dominant disorder caused by mutation in the *VHL* tumor suppressor gene located on chromosome 3p25–26. About 20% of patients with VHL disease have a *de novo* mutation of the gene.[5] The current patient is a sporadic case of VHL disease, and is confirmed by the *de novo* mutation of codon 161 in *VHL* gene. Codon 161 mutation is one of the most common germline mutation sites found in western and Japanese VHL families,[6] and has been reported in Chinese as well.[7] A previous study showed no association between the mutation point of *VHL* gene and the severity of RCH,[8] but the visual prognosis of RCH may be worse in patients with definite VHL disease than in those without VHL disease.[9]

The prevalence of RCH in patients with VHL disease ranged from 49% to 85%, and one third of them harbor multiple RCHs.[1] Histopathologically, the RCH is composed of abnormal capillary-like fenestrated channels surrounded by vacuolated foamy tumor cells. The capillaries become incompetent gradually, causing progressive exudation which may result in macular exudation or exudative RD and thus

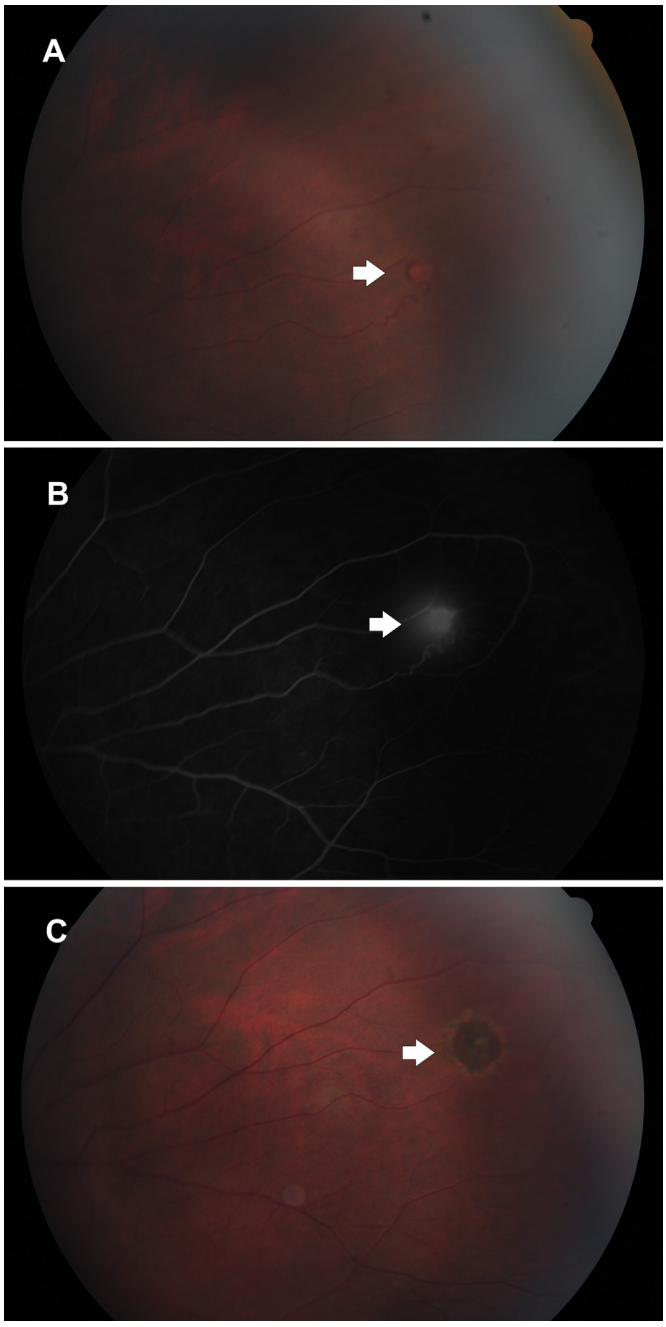

Fig. 4. (A) One of the four small retinal capillary hemangiomas in the left eye; (B) fluorescein angiography showed dye leakage from the tumor; and (C) the tumors regressed to tiny gliotic nodules after focal laser photocoagulation.

impair visual function.[1] Multiple tumors in different growing stages can be found in a single patient as in our patient. In the left eye, the four RCHs were small and were not complicated with subretinal fluid, whereas the three RCHs in the right eye were large and complicated with massive exudation. The small RCHs in the left eye were treated successfully with laser photocoagulation without any complication. Laser photocoagulation is effective in treating RCH smaller than 1.5 mm with peripheral location and clear media.[2]

In recent years, PDT has been used in treating large peripheral RCH with satisfactory results. Extensive literature

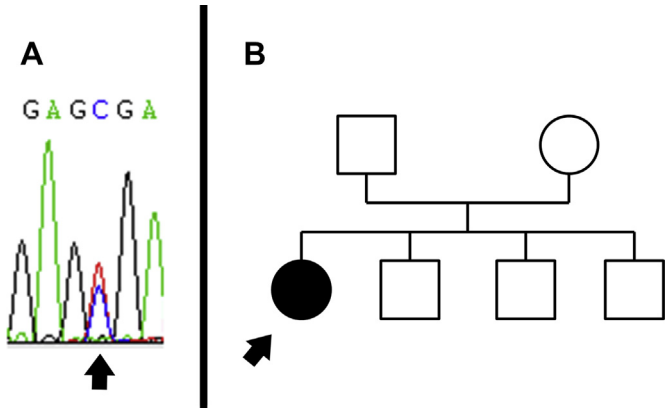

Fig. 5. (A) Genotyping of the *VHL* gene of the patient's DNA showed a transition mutation of C → T at nucleotide 694 (arrow), resulting in a nonsense mutation of Arg161stop in codon 161; and (B) genotyping of the patient's family member showed no mutation in the *VHL* gene.

review found 15 cases of peripheral RCH treated with PDT, including five cases of VHL disease, and most tumors regressed eventually with decreased exudation.[3,10–18] Among the reports, acute worsening of cystoid macula edema has been reported in a case of peripheral RCH treated with PDT, and resolved at 3 weeks after IVTA.[12] Transient increase in subretinal fluid and subretinal hemorrhage was reported in another three cases of peripheral RCH treated by PDT, and all resolved spontaneously within several weeks without intervention.[11,17,18] On the contrary, our case experienced persistent massive exudation after PDT, despite aggressive treatments with oral prednisolone, IVB, and IVTA. This is the first reported case of multiple peripheral RCHs treated by PDT and IVB, in which the tumors regressed satisfactorily, however, with persistent exudative RD that required surgical intervention.

Acute posttreatment exudation after PDT has been widely discussed. Although PDT can bring along significant vascular closure, vascular hyperpermeability and extravasation happen in the acute posttreatment stage.[19] PDT can also result in acute closure of the physiological choriocapillaris, causing choroidal ischemia and exacerbating the posttreatment exudation.[20] The massive subretinal exudation in this case, may be due to the summation reaction of three large tumors to PDT, instead of one tumor, as in other reports. Solitary RCH treated with PDT did not show extensive exudation, even with extended laser exposure time (166 seconds) or multiple laser spots covering the tumor and the feeding and draining vessels.[10,16] We therefore suggest that fractionated PDT may be used in cases with multiple RCHs in which one tumor is treated at a time to reduce the posttreatment reaction. Furthermore, IVTA may be used in combination with PDT to reduce the tumor reaction. Although bevacizumab has the effect of decreasing exudation by improving the barrier function, as an antivascular endothelial growth factor, however, the anti-inflammatory effect may be inferior to that of corticosteroids.

In conclusion, we have reported a rare case of VHL disease with multiple peripheral RCHs treated by PDT combined with IVB, which showed significant tumor regression but persistent exudative RD that required surgical intervention. The massive

exudation in this case may be due to the summation reaction of three large RCHs to PDT. Further studies are warranted to establish the optimal treatment for multiple RCHs.

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