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Original Article

Fundus imaging features of massive hemorrhaging in polypoidal choroidal vasculopathy after treatment

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Abstract: To explore the fundus imaging features of massive subretinal or vitreous hemorrhages in polypoidal choroidal vasculopathy (PCV) patients after treatment. This is a retrospective, non-controlled clinical study. We collected 9 PCV patients (9 eyes) with more than 6000 μm subretinal or vitreous massive hemorrhaging. Two patients who underwent combination therapy had massive subretinal hemorrhage (MSH) at day 75 and 82 post-treatment. Three patients who underwent PDT alone had MSH on postoperative day 22, 25 and 60. In addition, among four patients who underwent intravitreal injection of Conbercept alone, one patient developed MSH on day 30 after injection, while the other 3 patients suffered from vitreous hemorrhaging on day 1, 3 and 12 after injection, respectively. OCT showed several hill-shaped pigment epithelium detachments (PED), subretinal hyperreflective mass and cystoid hyporeflection fluid. FFA showed three hyperfluorescent spots in the early phase and gradually enhanced, diffused in the late phase. Visual acuity of 7 patients with MSH was improved after medical treatment. However, the visual acuity of another two patients with vitreous hemorrhaging showed no improved in one patient and slightly improved in another patient by vitrectomy. Therefore, the risk of subretinal and vitreous hemorrhaging in PCV patients was higher when the lesions were more than 6000 μm after PDT alone or in combination with anti-VEGF therapy.

Keywords: Polypoidal choroidal vasculopathy (PCV), photodynamic therapy (PDT), anti-vascular endothelial growth factor (Anti-VEGF), massive subretinal hemorrhage (MSH), vitreous hemorrhage (VH)

Introduction

Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi in 1982 and was termed as idiopathic polypoidal choroidal vasculopathy (IPCV) in 1990 [1]; following which, it was named as PCV according to the pathological characteristics [2, 3]. PCV occurs predominantly in pigmented races, that is, Asians and African-Americans compared to Caucasians [4, 8].

It is exudative retinopathy characterized by orange-red subretinal lesions, abnormal branched vascular network, and polypoid lesions with an enlarged distal portion, in addition to having recurrent retinal hemorrhaging, exudative retinal detachment, serous or hemorrhagic pigmented epithelial detachment (PED). Polypoid lesions occur in all parts of the retina and are primarily localized outside or under the central fovea of the macula [5]. Presently, ICGA is considered the gold standard in diagnosing PCV, because it shows the hyperfluorescent polypoid lesions with or without abnormal branched vascular network [6].

Treatment strategies for PCV include photodynamic therapy (PDT), anti-VEGF therapies, combination therapy of PDT with anti-VEGF, retinal laser photocoagulation and transpupillary thermotherapy [7, 8]. Among them, retinal photocoagulation is applicable for lesions outside the central fovea and is effective for a majority of the PCV patients. However, PDT or intravitreal anti-VEGF injection is used for a lesion under the central fovea, which can control and alleviate the conditions of most patients. Some stud-

ies reported that PCV patients developed massive subretinal or vitreous hemorrhaging after undergoing PDT alone or in combination with anti-VEGF therapy and explored the underlying mechanisms [9].

In this study, 220 PCV patients who underwent PDT alone or anti-VEGF alone or the combination of both were analyzed in a retrospective study from July 2015 to June 2018, and 9 patients (9 eyes) were enrolled in this study due to their eyes developing massive subretinal or vitreous hemorrhaging at different time points after treatment. Meanwhile, cytokines in the aqueous humor of some patients were measured, and the correlations are explored. The fundus imaging features and therapeutic effects are reported as follows.

Materials and methods

This was a retrospective, non-controlled clinical study. A total of 220 PCV patients who underwent PDT or anti-VEGF, or the combination of both were analyzed in a retrospective study from July 2015 to June 2018, and 9 patients (9 eyes) were enrolled in this study due to their eyes developing massive subretinal or vitreous hemorrhaging at different time points after treatment. Four patients were male and 5 patients were female. Ages ranged from 45 to 72 years old (average 61.78 y). The postoperative hemorrhage date ranged from 1 to 82 days (average 38.11 d). The preoperative visual acuity ranged from 0.01 to 0.2 (average 0.07). The final visual acuity ranged from 0.01 to 0.4 (average 0.18). Among the 9 patients, 2 patients underwent PDT followed by treatment with intravitreal injection of Lucentis after 2 weeks; 3 patients underwent PDT, and 4 patients were administered intravitreal injection of Conbercept. The items including visual acuity test, intraocular pressure test, slit-lamp microscopy, optical coherence tomography (OCT), and color fundus photography were performed in 9 patients at eight time points including pre-operation at 1 week and post-operation on day 1, 7, 14 and month 1, 2, 3, 6; while FFA combined with ICGA was performed before operation and postoperative month 1 and 6.

PDT treatment method

First of all, Verteporfin (Novartis PhamaSchweiz AG, Switzerland) was prepared according to the manufacturer's instructions: Verteporfin was prepared into a 7.5 ml solution at a concentration of 2 mg/ml using 7 ml of sterile water for injection. After the precise measurement of the patient's height and body weight, the prepared Verteporfin was solubilized into 5% glucose solution at a dose of 6 mg/m^2 body surface area in a 30 ml solution. Using the appropriate injection pump and filter, the solution was infused intravenously within 10 min at a rate of 3 ml/min. After 15 min post-infusion, the ocular lesion was irradiated with a 689 nm non-thermal diode laser at a dose of 50 J/cm^2 and a laser intensity of 600 mW/cm^2. In order to ensure the full coverage of the lesions by the facula, the size of the facula in the laser therapy was at the maximum linear distance of the lesion increased by 1000 μm. The dose was used up within 83 s of irradiation, and patients were advised to avoid light for 48 h postoperatively.

Intravitreal injection of anti-VEGF method

Before PCV patients entered the operating room, Alcaine eye drop was applied twice. Subsequently, the patient was laid on the operating table. Then, 0.5% povidone-iodine (Shanghai Likang Co, Ltd.) was used for the local disinfection of the eye, followed by the disinfection of the eyelashes with normal protection. Then, an eyelid opener was used for opening the eyes, and 0.05% povidone-iodine was used to rinse the conjunctival sac. After 60 s, 2% Lidocaine was used to rinse the conjunctival sac, and then, 0.05 mL of Lucentis (Novartis Pharma Schweiz AG) or Conbercept (Chengdu Kanghong Biotechnology Co, Ltd.) was injected into the vitreous cavity by inserting a needle at 4 mm behind the corneoscleral junction. Furthermore, an insulin needle was used for anterior chamber puncture at the corneal limbus, and 0.05 mL of anterior chamber fluid was extracted in order to balance the intraocular pressure immediately. After the needle was pulled out, hemostasis by compression was performed for 1-3 minutes. After the operation, TobraDex ointment was applied to the conjunctival sac, and the operative eye was covered. The re-examination was performed the next day.

Combination therapy

Two patients underwent PDT after a definite diagnosis. After 1 week, they were treated with

Table 1. Baseline data

Demographic	data
Number of subjects	9
Sex (male:female)	4:5
Age (y)	61.78±8.15
Bleeding time (d)	38.11±31.84
Pre-op BCVA (logMAR)	0.07±0.06
Final BCVA (logMAR)	0.18±0.16
Hypertension (numbers of subjects)	4

intravitreal injection of anti-VEGF similarly as mentioned above.

Results

Massive subretinal or vitreous hemorrhaging occurred in 9 patients at different time points after treatment. Two patients developed subretinal hemorrhages on day 75 and 82 after combination therapy, and 3 patients developed it on day 22, 25 and 60 after PDT alone. Furthermore, among the 4 patients treated with intravitreal injection of Conbercept alone, 1 patient developed subretinal hemorrhaging on day 30 after operation, while the other 3 patients developed vitreous hemorrhaging on day 1, 3, and 12 after operation. All the patients were followed up on day 1, 7, 14 and 1, 2, 3, 6 months for a total of seven-time points.

Interestingly, massive subretinal or vitreous hemorrhaging was mostly absorbed in 7 patients after taking medication. Their BCVA was improved from 1.02±0.65 logMAR preoperatively to 1.17±0.48 logMAR postoperatively at month 6 postoperatively. Two patients with massive vitreous hemorrhaging were treated with vitrectomy, and their visual acuity changed from 0.05 and 0.03 preoperatively to 0.01 and 0.3 at month 6 postoperatively, respectively. Endophthalmitis or ocular and systemic complications were not found in any of the patients during the follow-up (**Tables 1**, **2**).

Among the nine patients, there are two special patients who were observed carefully. One was a 59-year-old male, who suffered from hypertension for 8 years. BCVA of his right eye was 0.1; the IOP was normal. The anterior segment of the eye was normal and a subretinal hemorrhage was observed. OCT showed several hill-shaped pigment epithelium detachments (PED), subretinal hyperreflective mass and cystoid hyporeflection fluid. FFA showed three hyperfluorescent spots in the early phase and gradually enhanced, diffused in the late phase. The intravitreal injection of Conbercept was performed 17 days later. As a result, the visual acuity dropped quickly after injection 1 day, which was only the count finger, and moderate hemorrhaging in the vitreous was observed. After medical treatment, the BCVA of the right eye recovered to 0.03 on day 12 postoperatively and 0.1 on day 60 postoperatively. Fundus hemorrhaging was gradually absorbed, the patchy yellow scar-like lesions were only observed in the macular region at the 6 months postoperatively. The fundus of left eye was normal. See to **Figures 1**-**3**. Another special patient was a 68-year-old female patient. The BCVA of her left eye was 0.12. The intraocular pressure and the anterior segment of the left eye were normal. Small patchy hemorrhage and exudation, as well as extensive dome-shaped yellowish-white edema, were observed in the posterior pole of the fundus. Autofluorescence showed enhanced fluorescence in the macular region. Angiography showed that the lesion area with about 8 DD of macula always presented hypofluorescence. Moreover, thickened and enhanced dot-like hyperfluorescence were only observed in the central of the macular and the nasal lateral in the late phase; no diffusion was observed. FFA showed that the cap-like hyperfluorescent region was noted at the central fovea. Hypofluorescence of lesion area was found from ICGA. See to **Figures 4**, **5**.

Discussion

The pathogenesis of PCV is still unclear and severe complications such as massive subretinal hemorrhaging, vitreous hemorrhaging and retinal tearing might occur solely or simultaneously after treatment. The underlying pathogenesis might be related to the size, location of PCV lesions, the time of first diagnosis and duration of treatment as well as whether it is combined with hypertension or diabetes or whether anticoagulant drugs are used. The mechanisms of hemorrhaging may be as follows:

The first mechanism is mechanical pressure. Lafaut et al. enucleated the eyeballs of PCV patients to perform histological examinations and found that dilated thin-wall vessels were saccular on serial sections, while some were

Table 2. Clinical data of patients

Case	Sex	Age (y)	Treatment methods	Bleeding time (d)	Complications	Pre-op BCVA	Final BCVA	PPV[1]	Systemic diseases
1	M	65	PDT+Lucentis	75	MSH[2]	0.01	0.1	No	Diabetes
2	M	69	PDT+Lucentis	82	MSH	0.02	0.3	No	Hypertension
3	F	72	PDT	25	MSH	0.2	0.4	No	Hypertension
4	M	60	PDT	22	MSH	0.1	0.4	No	None
5	F	68	PDT	60	MSH	0.12	0.1	No	Diabetes
6	F	45	Conbercept	3	MSH+VH[3]	0.05	0.01	Yes	None
7	M	59	Conbercept	1	MSH+VH	0.04	0.01	No	Hypertension
8	F	56	Conbercept	12	MSH+VH	0.03	0.3	Yes	Diabetes+Hypertension
9	F	62	Conbercept	63	MSH	0.1	0.04	No	None

[1]PPV: posterior polar vitrectomy; [2]MSH: Massive Subretinal hemorrhage; [3]VH: Vitreous hemorrhage.

localized almost immediately under the diffuse drusen [10], which indicated that the PCV lesion had a high tendency to hemorrhage. After anti-VEGF drugs were injected into the vitreous cavity, the intraocular pressure will rise transiently, choroidal vessels will be compressed, leading to the blood breaking through abnormal blood vessels with high permeability and thin walls. This phenomenon could result in massive subretinal hemorrhages, which is consistent with the hemorrhaging coming from cases 6-9 of our patients (**Table 1**) after they underwent the intraocular anti-VEGF injection. In addition, as a kind of photoactive drug for vascular occlusion, Verteporfin is injected intravenously when PCV patients undergo PDT. After polypoidal lesions were irradiated with 689 nm red light, abnormal blood vessels were occluded. The blood flow in these vessels is compressed into the concealed abnormally dilated blood vessels, and when their carrying capacity is exceeded, shear force is exerted on the RPE cells that are attached to the Bruch membrane. Subsequently, RPE tearing occurs leading to massive subretinal hemorrhaging. Hemorrhaging in our fifth case is related to this mechanism directly.

The second mechanism is hemodynamics. The disorders of choroidal venous circulation lead to polypoidal changes of blood vessels and choroidal stasis is speculated as the main cause of PED in PCV [11]. After PDT is performed, choroidal venules with stasis might rupture and bleed due to suddenly hemodynamic changes. Hirami et al. observed that if a small amount of the hemorrhage was absorbed, it would have little effect on visual acuity. However, if a massive vitreous hemorrhage occurs, it would have a greater effect on visual acuity [12]. In this study, the patient in typical case 1 developed a massive vitreous hemorrhage. Although this patient underwent vitrectomy promptly, his visual acuity only recovered to 0.01 because subretinal hemorrhaging persisted in the macular region. Moreover, it was rare for patients to develop spontaneous vitreous hemorrhaging after PCV treatment and was secondary to subretinal hemorrhage [13]. In the typical case 1 of this study, subretinal hemorrhaging occurred on day 1 after treatment and vitreous hemorrhaging occurred on day 12 after treatment, which was consistent with the observations of the studies mentioned above conducted in other countries. In experiments in rabbit eyes, vitreous hemorrhaging mostly occurred in the thick subretinal hemorrhages. Furthermore, extensive necrosis was observed in all the retinal layer structures under the microscope. However, the inner limiting membrane was intact. The red blood cell membrane fragments enter into the vitreous body through the intact inner limiting membrane, resulting in vitreous hemorrhaging [14]. This finding was consistent with our current result that no retinal tear was detected, and the inner limiting membrane was intact in two patients with hemorrhaging after undergoing vitrectomy.

The third mechanism is the inflammatory cytokines. Previous studies demonstrated that various inflammatory cytokines including C-reactive protein, interleukin, monocyte chemoattractant protein-1, VEGF, and inducible protein (IP)-10 were related to the pathogenesis of PCV [15-18]. Zhang et al. found that intravitreal injection of Triamcinolone acetonide alone was superior to anti-VEGF therapy alone in the treatment of PCV combined with hemorrhagic retinal detach-

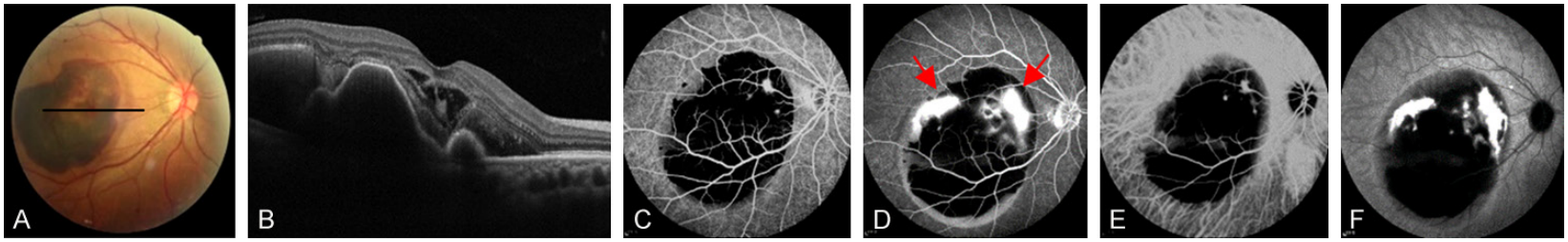

Figure 1. Preoperative fundus imaging. A: Preoperative CFP of the right fundus showed that a massive subretinal hemorrhage was observed in the macular region; light yellow lesions are seen in the center of the hemorrhagic region. B: Preoperative OCT showed that many PEDs were hill-shaped accompanied by subretinal hyperreflective mass and cystoid hyporeflection fluid. C-F: FFA showed 3-4 hyperfluorescent spots in the paramacular of the right eye in the early phase. The spots were fused and diffused in the late phase and presented as strip-like hyperfluorescence (red arrow). Blocked fluorescence was observed in the other massive hemorrhagic region.

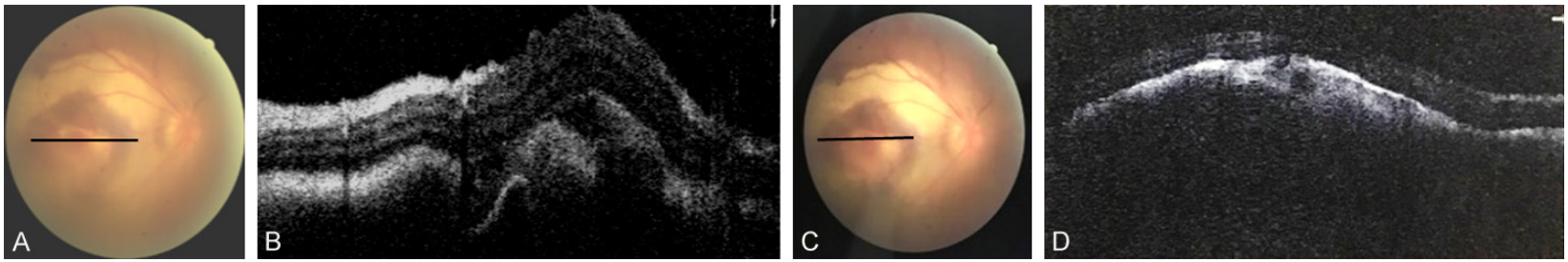

Figure 2. Fundus imaging on postoperative days 1 and 12. A, B: CFP showed a vitreous hemorrhage. OCT showed that retinal layer structures were unclear and thickened at the macular area due to unclear refractive medium. C, D: CFP showed that a vitreous hemorrhage was partly absorbed and the region of fundus hemorrhaging was reduced. OCT showed that many hill-shaped uplifts hemorrhages disappeared and substituted by arched ones.

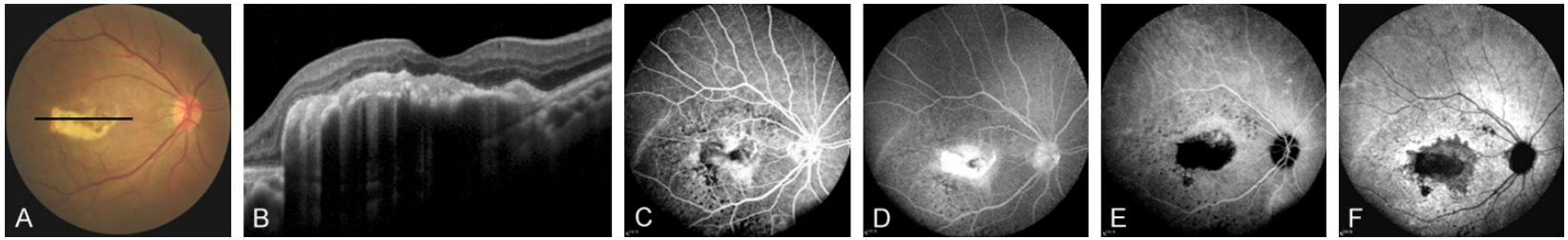

Figure 3. Fundus imaging features at postoperative month 6. A: CFP showed that a yellowish-white scar was formed in the macular region. B: OCT showed that flatted hill-shaped hyperreflective bump was observed in the macular region accompanied by a large area of hypofluorescence. C, D: FFA showed a hyperfluorescent mass in the center of the lesion accompanied by mottled-like fluorescence at the periphery of lesion. E, F: ICGA showed irregular hypofluorescence in the center of the lesion accompanied by hyperfluorescent halo at the periphery of the lesion.

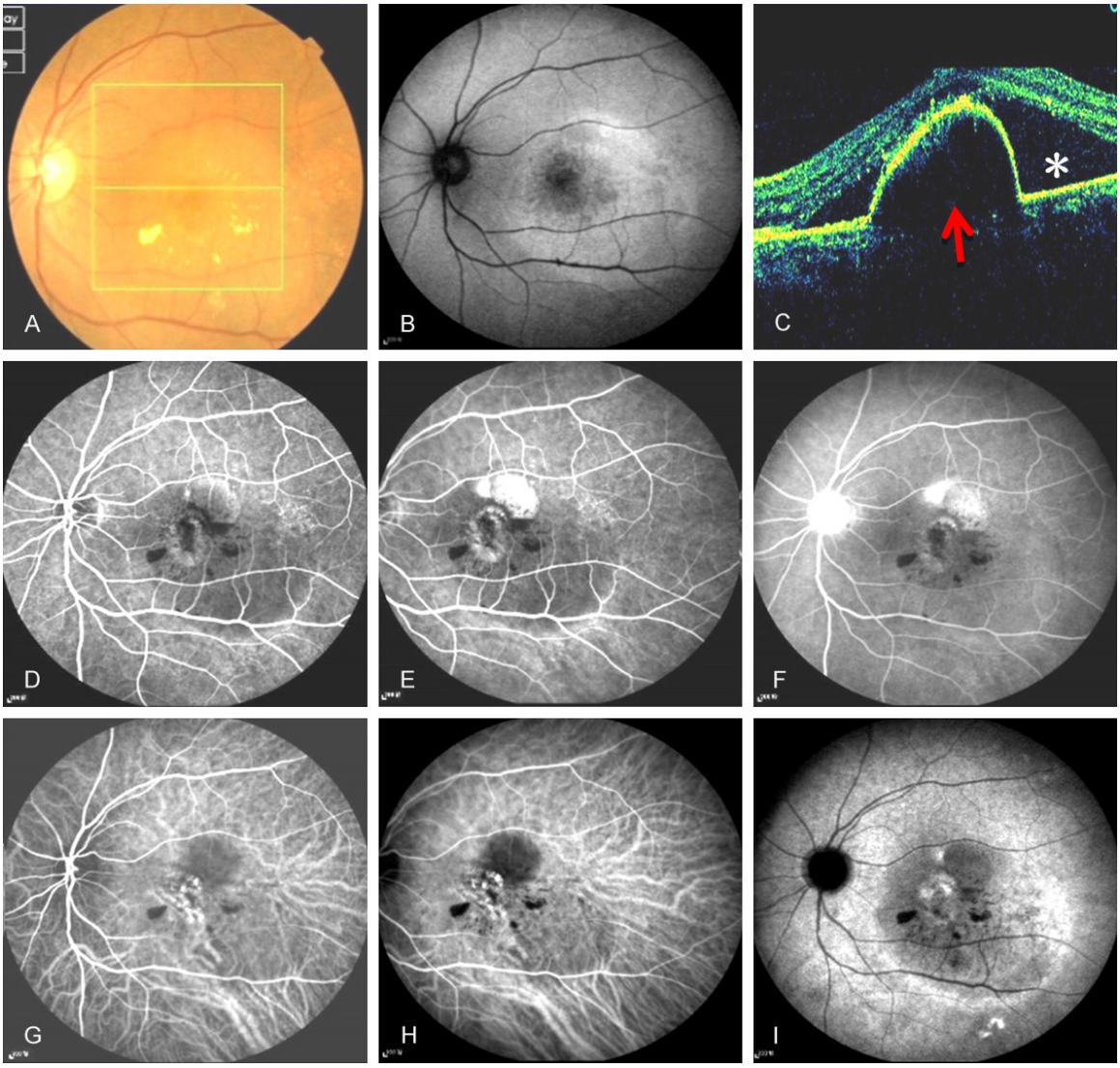

Figure 4. Preoperative fundus imaging. A: CFP showed a small patchy hemorrhage and exudation as well as extensive dome-shaped yellowish-white edema around the macula. B: Autofluorescence showed enhanced fluorescence in the macular region (about 8 DD); small patchy hypofluorescence was observed near the central fovea. C: OCT showed that subretinal exudation (white asterisk) presented a hyporeflection accompanied by a hill-shaped PED (red arrow). D-F: Early-, middle- and late-phase retinal fluorescein angiography showed that the lesion with about 8 DD of the central fovea of macular always presented hypofluorescence; thickened and enhanced hyperfluorescence was only observed at or above the central fovea of the macular in the late phase; no obvious diffusion was observed. G-I: Early-, middle-, and late-phase choroidal fluorescein angiography showed that the lesion in the central fovea of macular presented dot- and mottled-like fluorescence; the circular lesion above the central fovea always presented hyperfluorescence; the lesion on the posterior pole (about 7 DD) presented hypofluorescence in the late phase, and a hyperfluorescence halo can be seen around the lesion.

ment. The study also confirmed that PCV was closely related to inflammatory cytokines [19]. In the present study, cytokines in the aqueous humor of some patients were also detected. For example, the intraocular concentrations of IL-6 in the typical case 1 of a PCV patient were 11.96, 11.48, and 13.03 pg/mL, respectively after three injections, with little differences, thereby indicating that the role of inflammatory factors in the pathogenesis of PCV could not be controlled by anti-VEGF injection alone. The current results fully demonstrated that PCV was a neovascular disease that might involve inflammatory factors or other factors. Therefore, before and after PCV patients undergoing PDT alone or in combination with anti-VEGF therapy,

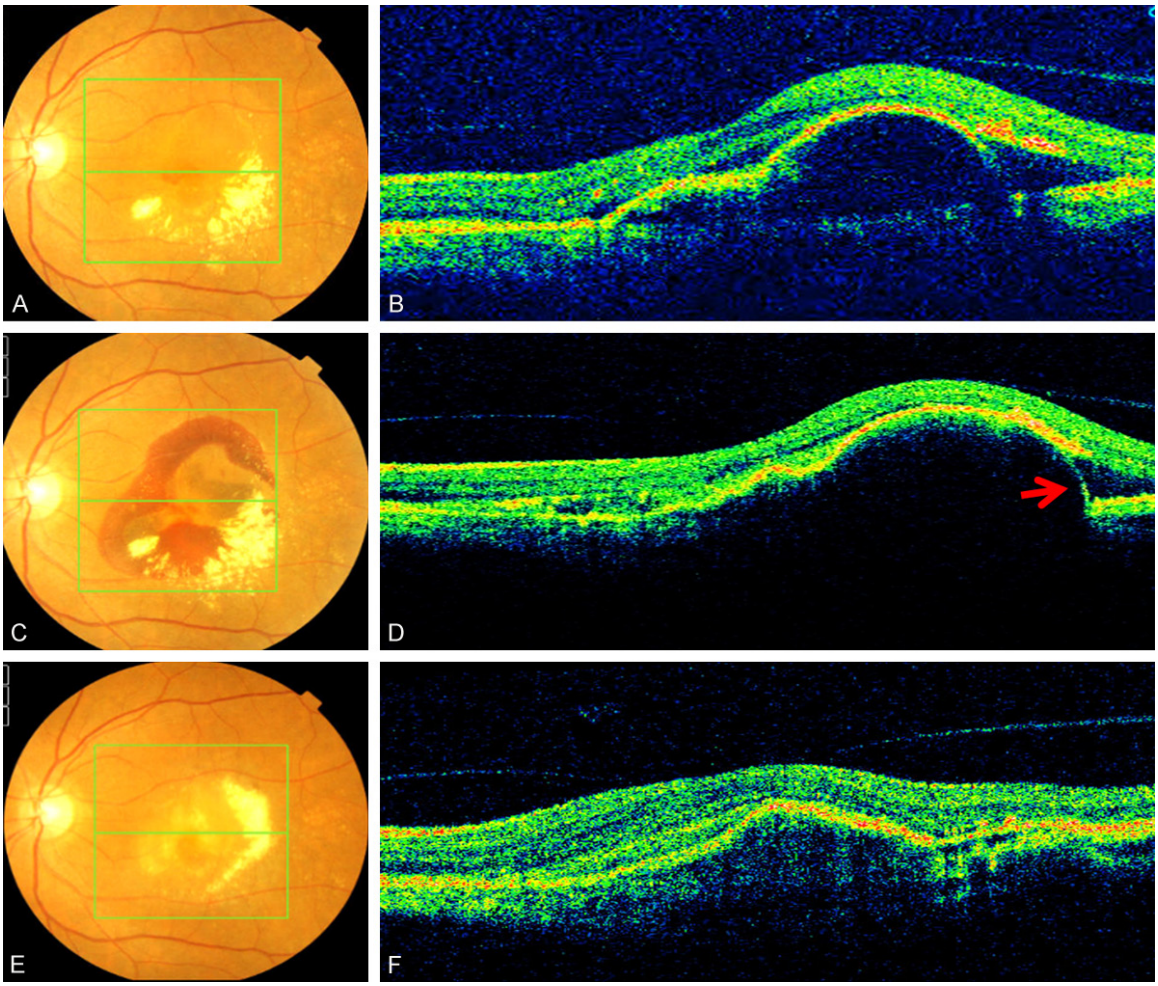

Figure 5. Preoperative fundus imaging. A, B: At month 1 after PDT, the macular lesion shrank slightly, the hemorrhage disappeared, and the exudation increased slightly. OCT showed that most of the subretinal fluid (SRF) disappeared; hill-shaped PEDs shrank and became flattened. C, D: At 2 months after treatment, the macular hemorrhage and exudation increased significantly. OCT showed that the retinal pigmented epithelium (RPE) was discontinuous and torn (red arrow); subretinal exudates can be seen; the range of PED was enlarged; bumps were slightly elevated. E, F: At month 6 post-treatment, the macular hemorrhaging was absorbed basically, and yellowish-white scar-like lesions are observed. OCT showed that the SRF was disappeared, the PED shrank, and the torn RPE was partially connected.

intraocular inflammatory cytokines affect the stability of the blood-retina barrier, thereby altering the vascular permeability and leading to massive subretinal or vitreous hemorrhaging.

The fourth mechanism is systemic factors. Shin et al. demonstrated that the condition of the eye lens, hypertension, and diabetes had little effect on the risk of hemorrhaging in PCV patients after treatment as most patients with vitreous hemorrhages were administered anticoagulant drugs for several months before the treatment [20]. Talany et al. found that the use of Warfarin, Dabigatran, and Rivaroxaban increased the risk of intraocular hemorrhaging [21]. Of the 9 PCV patients in this study, 1 patient had hypertension and diabetes, 2 patient presented diabetes alone, and 3 patients had only hypertension. Some of the patients often ingested anticoagulants or antiplatelet drugs such as Warfarin and Aspirin. Therefore, whether massive hemorrhaging in these patients is related to systemic diseases and medication is uncertain necessitating the observation and study of additional cases.

In conclusion, the size, location, and thickness of PCV lesions as well as the patient's general condition before the operation should be care-

fully considered when PDT alone or in combination with anti-VEGF therapy is performed in PCV patients. In addition, appropriate treatment time and therapeutic regimens were formulated in order to minimize the risk of subretinal and vitreous hemorrhaging and maximize the recovery of visual acuity and visual function.

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Disclosure of conflict of interest

None.

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