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Original article

Visual prognosis of massive submacular hemorrhage in polypoidal choroidal vasculopathy with or without combination treatment

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Abstract

Background: Submacular hemorrhage associated with polypoidal choroidal vasculopathy (PCV) may cause severe visual loss. The purpose of this study is to report the visual prognosis of massive submacular hemorrhage in patients with PCV.
Methods: Twenty patients with PCV and submacular hemorrhage who received either subretinal tissue plasminogen activator (TPA) with vitrectomy or intravitreal injection of TPA and gas to achieve pneumatic displacement of the hemorrhage were enrolled. Additionally, combination treatment with either photodynamic therapy (PDT) or intravitreal injection of vascular endothelial growth factor inhibitors (anti-VEGF) was performed to treat the underlying PCV.
Results: Five patients received subretinal TPA with vitrectomy and 15 patients received intravitreal injection of TPA and gas to remove or displace the submacular hemorrhage. Combination treatment with PDT and intravitreal anti-VEGF was performed in three patients and intravitreal anti-VEGF injection alone in 13 patients. The mean logarithm of the minimal angle of resolution converted from the best corrected visual acuity (BCVA) were improved at 3 months, 6 months, and 12 months. Better initial BCVA, smaller size of submacular hemorrhage and younger age were statistically significant predictors for BCVA. Combination treatment with PDT showed significant efficacy in the improvement of BCVA.
Conclusion: Combination treatment of submacular hemorrhage secondary to PCV may yield visual and anatomic improvements. Initial BCVA, the initial size of submacular hemorrhage and age were significant predictors for visual prognosis.

Keywords: combination treatment; photodynamic therapy; polypoidal choroidal vasculopathy; submacular hemorrhage; vascular endothelial growth factor inhibitors

1. Introduction

Submacular hemorrhage may cause sudden visual loss and the prognosis is guarded. The mechanism is thought to be due to iron toxicity, the shear stress of photoreceptors by fibrin clots and the physical separation of photoreceptors from the retinal pigment epithelium (RPE).[1−7] The etiology of submacular hemorrhage is most commonly neovascular age-related macular degeneration (AMD), but polypoidal choroidal vasculopathy (PCV), retinal artery macroaneurysm, trauma, presumed ocular histoplasmosis syndrome, and high myopia have also been reported.[2,3,6−8] PCV is prevalent in 10−54% of the Asian patient population and accounts for 24.5% of patients with neovascular AMD in the Chinese population.[9,10] Moreover, the incidence of sub-RPE or

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subretinal hemorrhage is high (30–64%) in PCV patients. In addition, although photodynamic therapy (PDT) had proved to be effective in regressing polyps (reference of EVEREST), the complication rates of subretinal hemorrhage were high at 6.5%.[11,12]

Dense submacular hemorrhage may mask the underlying lesion and limit the information that can be obtained from angiography. It can also impede and reduce the effect of treating the underlying lesion.[8,13] Thus, the management options should include surgical submacular clot evacuation or pneumatic displacement followed by treatment with intravitreal injection of vascular endothelial growth factor inhibitors (anti-VEGF) with or without PDT, depending on the activity of the polyps and if the polyps could be located with image study.[1–6] There is no consensus regarding the factors that influence the outcome of submacular hemorrhage in PCV patients. Hence, the present study aims to compare different treatment options and to evaluate the visual prognosis in submacular hemorrhage patients after blood displacement.

2. Methods

Medical records of 56 patients diagnosed with submacular hemorrhage who received treatment by the same surgeon (S.J.C.) between January 2005 and March 2012 were reviewed retrospectively. The etiology of submacular hemorrhage among this group was 53.6% neovascular AMD ($n = 30$), 35.7% PCV ($n = 20$), 5.4% retinal artery macroaneurysm ($n = 3$), 1.8% trauma ($n = 1$), and 3.6% high myopia ($n = 2$). Detailed information and ophthalmologic examination results included: patient history, sex, age at presentation, affected eye, the presence of duration, the initial size of submacular hemorrhage, initial best corrected visual acuity (BCVA), and fluorescein and indocyanine angiography. Optical coherence tomography (OCT) was also performed at the initial visit to determine whether RPE detachment occur with the submacular hemorrhage. The diagnosis of PCV was made and categorized into two subgroups which were defined by Tanaka et al[14] and Yuzawa et al[15] based on the indocyanine green angiography (ICGA) findings. ICGA was performed at the initial visit or after the hemorrhage had been displaced. In the first subgroup, both feeder and draining vessels are visible on ICGA and network vessels are numerous, this is then defined as polypoidal choroidal neovascularization (CNV). The second subgroup was thus defined as PCV in narrow sense with neither detectable feeder nor draining vessels, and small network numbers (Fig. 1). Among the 20 eyes in 20 patients diagnosed with PCV, four were polypoidal CNV and 16 were PCV in narrow sense enrolled in this study. Other exclusion criteria included: PCV patients who did not receive surgical submacular clot evacuation or pneumatic displacement and those who lacked a complete medical record and ophthalmic examination results. Patients who did not have follow-up for at least 1 year were also excluded.

Visual outcome was evaluated at 3 months, 6 months, and 12 months. Additional treatment with either PDT or intravitreal injection of anti-VEGF or both was determined using a monthly as-needed basis depending on the presence of subretinal fluid or macular edema. PDT with verteporfin infusion and laser application was performed using the half-fluence dose by decreasing the light exposure to 43 seconds. The anti-VEGF drugs used in this study were either ranibizumab (0.5 mg/0.05 mL) or bevacizumab (2.5 mg/0.1 mL). The injection was done in the operating room under topical anesthesia using a 30-gauge needle and injected 3.5–4.0 mm posterior to the limbus.

Complications of vitreous hemorrhage (VH) and the latest macula status such as RPE atrophy and disciform scar formation were analyzed.

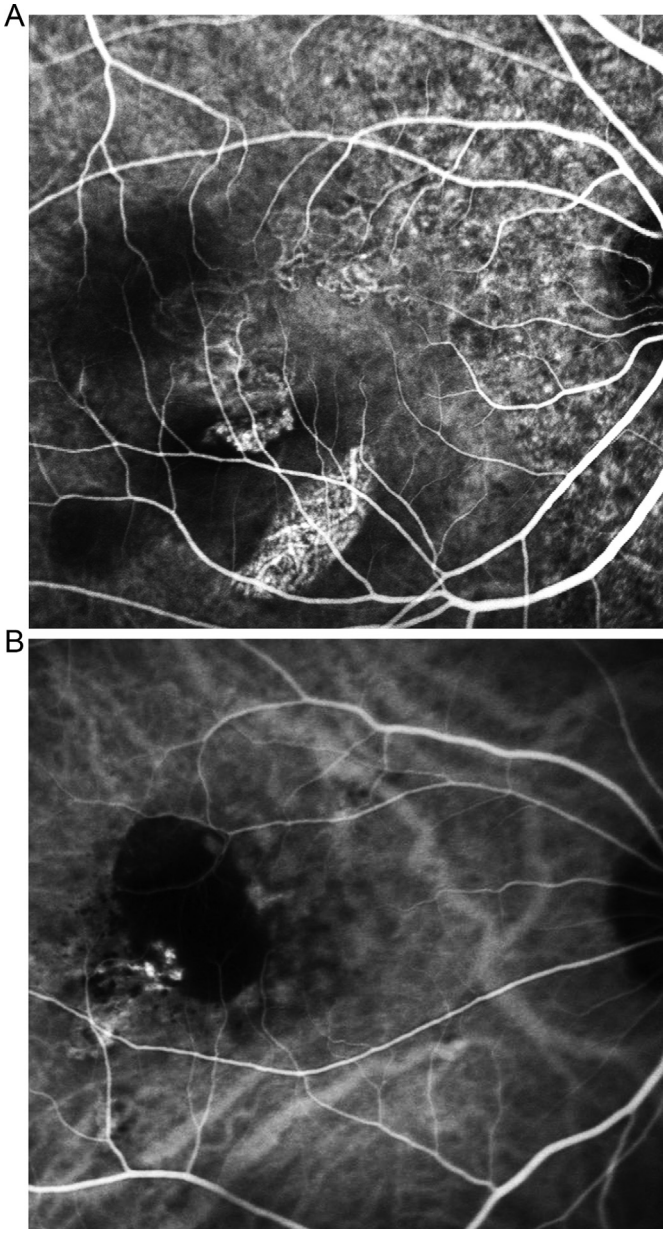

Fig. 1. (A) Numerous network vessles with multiple polypoidal lesions at periphery, defined as polypoidal choroidal neovascularization on indocyanine green angiography. (B) Indocyanine green angiography demonstrated polypoidal choroidal vasculopathy in narrow sense as small number of network vessel and several dilated polypoidal lesions.

Statistical analysis was performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). Wilcoxon rank-sum test, Kruskall–Wallis test, and Pearson correlation coefficient were used for data analysis. A p value < 0.05 was considered statistically significant.

3. Results

Twenty eyes of 20 patients met the inclusion criteria (Table 1). The mean age was 65.8 ± 14.4 years (range, 40–89 years), compared to 78.47 ± 5.6 years (range, 72–89 years) in those with AMD etiology eyes. Twelve patients were male and eight female. Six of the 20 patients had hypertension. The duration between hemorrhage presentation and treatment for blood displacement ranged from 1 day to 2 months with a mean of 14.3 ± 16.6 days. The mean initial size of submacular hemorrhage was 17.8 ± 19.2 disk diameter (DD) compared (2–64 DD) with the patient's own disc size according to preoperative color fundus photography.

Table 1
Demographic data of the patients with polypoidal choroidal vasculopathy (PCV) and massive submacular hemorrhage (SMH).

Characteristics	n	(%)
Sex		
Male	12	(60)
Female	8	(40)
Age (y)		
≤ 60	9	(45)
> 60	11	(55)
Affected eye		
Right	11	(55)
Left	9	(45)
Duration (d)		
≤ 14	15	(75)
> 14	5	(25)
Initial size of SMH (DD)		
≤ 10	12	(60)
> 10	8	(40)
RPE detachment		
Yes	13	(65)
No	7	(35)
Subgroup		
Polypoidal CNV	4	(20)
PCV in narrow sense	16	(80)
Surgical treatment		
Vitrectomy + intravitreal TPA	5	(25)
Intravitreal gas (SF6) + intravitreal TPA	15	(75)
Combine treatment with PDT		
Yes	3	(15)
No	17	(85)
Combine treatment with IVI anti-VEGF		
Yes	13	(65)
No	7	(35)
PCV in the fellow eye		
Yes	5	(25)
No	15	(75)
Hypertension		
Yes	6	(30)
No	14	(70)

CNV = choroidal neovascularization; DD = disk diameter; IVI = intravitreal injection; PDT = photodynamic therapy; RPE = retinal pigment epithelium; TPA = tissue plasminogen activator; VEGF = vascular endothelial growth factor inhibitors.

OCT showed a simultaneous RPE detachment within the hemorrhage lesion in 13 patients. The mean initial logarithm of minimal angle of resolution (logMAR) BCVA was 0.85 ± 0.65. Four polypoidal CNV and 16 PCV in narrow sense were defined based on ICGA findings with a mean initial logMAR BCVA of 0.68 ± 0.47 and 0.89 ± 0.70, respectively. Five patients under went vitrectomy with subretinal injection of TPA and air exchange followed by prone position.[4,5,16–18] Fifteen patients received TPA with pneumatic displacement of submacular hemorrhage by intravitreal injection of pure sulfurhexafluoride. The average submacular hemorrhage sizes were 33.6 DD and 12.5 DD in patients who underwent vitrectomy and pneumatic displacement respectively. All 20 patients except one showed either complete or partial displacement of the submacular blood from the foveal center. Combination with PDT was performed in three patients and intravitreal anti-VEGF injection alone in 13 patients. In six out of 13 patients, intravitreal anti-VEGF injection was performed at the same time during the pneumatic displacement operation. Furthermore, five of these six patients received further injection as needed on a monthly basis (Fig. 2). The mean logMAR BCVA improved from 0.85 ± 0.65 to 0.79 ± 0.62 at 3 months ($p = 0.005$), to 0.69 ± 0.65 at 6 months ($p = 0.002$), and to 0.63 ± 0.52 at 12 months ($p = 0.029$). Better initial BCVA, smaller initial size of submacular hemorrhage and younger age were statistically significant predictors for visual improvement at 3 months, 6 months, and 12 months (Table 2). Sex, systemic disease of hypertension, and the duration of submacular hemorrhage were not associated with the visual prognosis. Furthermore, combination treatment with PDT showed significant efficacy in the improvement of BCVA (Table 3). Small initial size of submacular hemorrhage showed statistically lower incidence following intravitreal anti-VEGF injection ($p = 0.002$).

The fellow eye was observed for the possibility of developing PCV during the follow-up period. In the five patients (25%) who developed PCV in the fellow eye, all were found to be associated with smaller initial submacular hemorrhage size ($p = 0.001$).

Compared to patients with PCV in narrow sense, those with polypoidal CNV had a better mean initial BCVA (0.68 ± 0.47 and 0.89 ± 0.70, respectively). However, two subgroups did not show any difference in visual prognosis or in treatment options to remove or displace the submacular hemorrhage. Polypoidal CNV patients even had BCVA deteriorate from 0.68 ± 0.47 to 0.83 ± 0.77 at 3 months, stationary at 0.83 ± 0.77 at 6 months and slightly improved to 0.80 ± 0.63 at 12 months. By contrast, PCV in narrow sense patients had BCVA improved from 0.89 ± 0.70 to 0.78 ± 0.61 at 3 months ($p = 0.012$), to 0.65 ± 0.64 at 6 months ($p < 0.001$), and to 0.59 ± 0.51 at 12 months ($p < 0.001$).

Thirteen patients (65%) showed an RPE detachment associated with the submacular hemorrhage lesion at the initial visit on OCT. However, RPE detachment showed no difference in either visual prognosis or in the incidence of receiving combination treatment. Complications of VH after the operation were noted in two patients. Both had spontaneous resolution that did not affect the visual outcome.

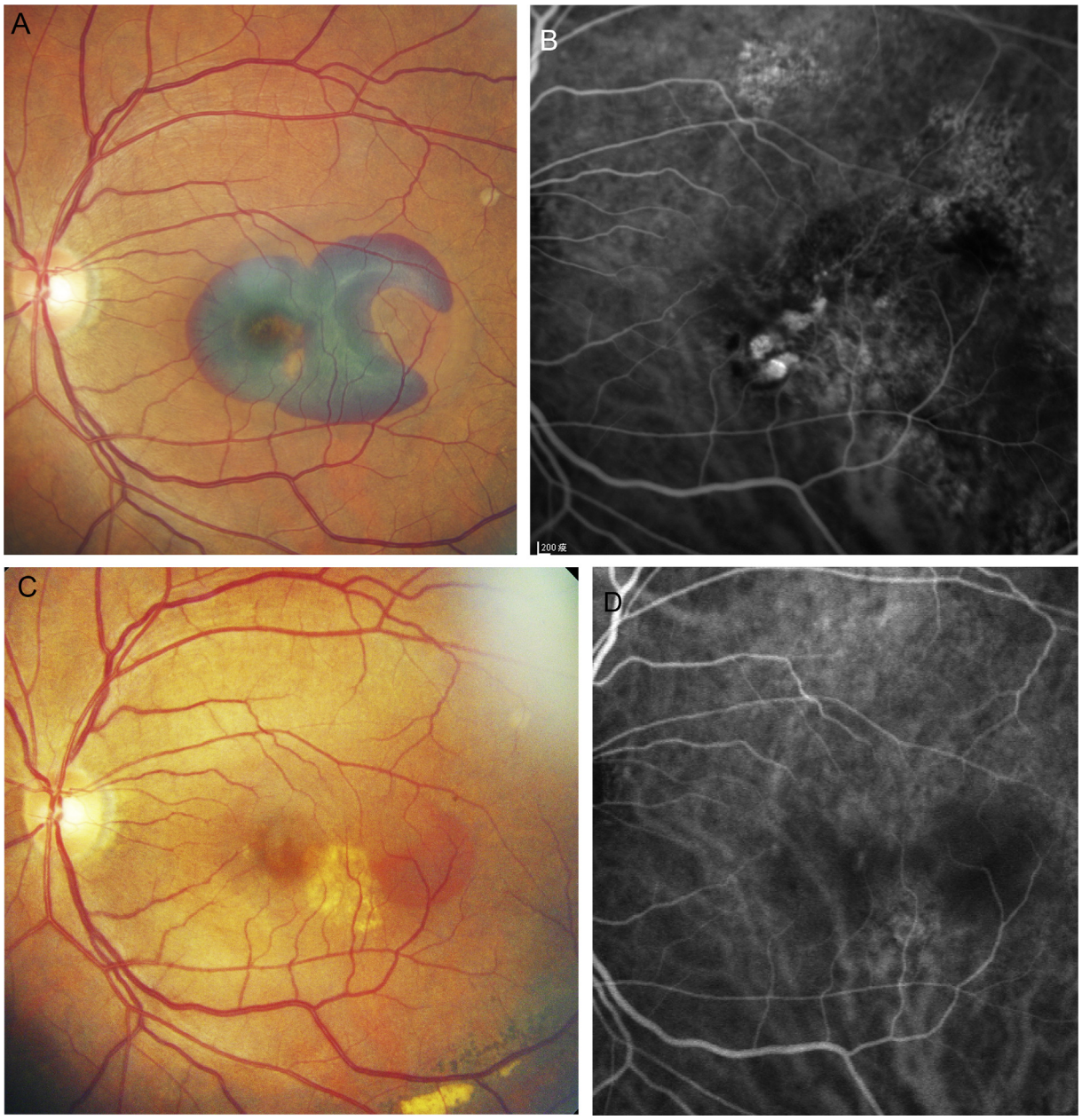

Fig. 2. Fundus photograph, indocyanine green angiography (ICGA) images before and after treatment. (A) Initial presentation of submacular hemorrhage. (B) ICGA at baseline demonstrates several polypoidal choroidal vasculopathy lesions. (C) At 3 months of follow-up, after pneumatic displacement, fundus photography shows displaced submacular hemorrhage with organized subretinal hemorrhage. (D) ICGA showed complete regression of polypoidal lesions 3 months after receiving combination treatment.

The mean follow-up time was 2.9 years (range, 1–8 years) and the latest macula states were evaluated throughout the follow-up period. As a result, 10 patients (50%) showed formation of a disciform scar, five patients (25%) RPE had atrophy, one patient developed a macular epiretinal membrane, and two patients showed persistent RPE detachment.

4. Discussion

The final visual outcome of submacular hemorrhage is poor. Although spontaneous resolution may occur over 1–15 months, degeneration of the inner and outer retinal layers as well as the RPE has been observed after hemorrhage in animal models.[7] As a result, early evacuation of the subretinal or sub-RPE blood is recommended. Furthermore, dense submacular hemorrhage may mask the underlying lesion and limit the information that can be obtained from angiography. It can also impede and reduce the effect of treating the underlying PCV because PDT diode lasers may not be able to penetrate the area, and anti-VEGF may not be able to diffuse through the thick blood clot.[6–8,13] Finally, because PCV lesions do not necessarily involve the fovea, surgical treatment

Table 2
Correlation coefficient of vision improvement and variables (univariate analysis).[a]

	Visual acuity at 3 mo		Visual acuity at 6 mo		Visual acuity at 12 mo	
	r	*p*	*r*	*p*	*r*	*p*
Age (y)	0.573	0.009*	0.622	0.002*	0.559	0.007*
Initial visual acuity (LogMAR)	0.601	0.003*	0.639	0.001*	0.487	0.013*
Initial size (disk diameter)	0.646	0.034*	0.699	0.044*	0.636	0.042*
Duration to treatment (mo)	0.168	0.224	0.201	0.124	0.313	0.074

mo = months.
* $p < 0.05$.
[a] Pearson's correlation coefficient test was used to test the association between variables and visual improvement.

of submacular hemorrhage may lead to good central vision.[16] However, the Submacular Surgery Trial reported disappointing outcomes and high complication rate after submacular surgery.[5,7] In 1996, Heriot proposed a simple and relatively noninvasive procedure of enzymatic liquefaction of submacular hemorrhage with TPA, followed by pneumatic displacement in.[2,5,7] Many retrospective case series have evaluated or compared the efficacy and safety of these two surgical procedures. The results showed that both surgical interventions appear to be favorable in management of submacular hemorrhage.[2,5,7,16–18] In a literature review, van Zeekes and van Meurs[18] even indicated that recent studies tended to use vitrectomy rather than pneumatic displacement. In our study, five patients (25%) underwent vitrectomy with TPA while 15 patients (75%) received TPA with pneumatic displacement using pure sulfurhexafluoride. All 20 patients except one showed either complete or partial displacement of the submacular blood. In the only case where pneumatic displacement failed, the submacular hemorrhage gradually absorbed and became a disciform scar after intravitreal injection of ranibizumab. In the other 19 patients, treatment options of either technique to remove or displace the submacular hemorrhage associated with PCV showed no difference in visual outcome which is similar to the report by Shiraga et al.[16]

PDT and anti-VEGF are the treatment options for PCV. PDT has been proven to stabilize the VA of PCV patients while anti-VEGF has been found to be effective in reducing the fluid from PCV lesions.[19] In the EVEREST study, PDT alone or combined with ranibizumab was superior to

Table 3
Associations of vision improvement and variables (univariate analysis).[a]

	Visual acuity at 3 mo		Visual acuity at 6 mo		Visual acuity at 12 mo	
	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*
Overall	0.79 ± 0.62	0.005*	0.69 ± 0.65	0.002*	0.63 ± 0.52	0.029*
Sex						
Male	0.90 ± 0.63	0.270	0.76 ± 0.67	0.473	0.67 ± 0.51	0.571
Female	0.63 ± 0.61		0.59 ± 0.64		0.56 ± 0.57	
RPE detachment						
Yes	0.72 ± 0.68	0.351	0.66 ± 0.71	0.643	0.58 ± 0.55	0.536
No	0.93 ± 0.53		0.74 ± 0.56		0.71 ± 0.50	
Subgroup						
Polypoidal CNV	0.83 ± 0.77	0.963	0.83 ± 0.77	0.820	0.80 ± 0.63	0.554
PCV in narrow sense	0.78 ± 0.61		0.65 ± 0.64		0.59 ± 0.51	
Combine PDT						
Yes	0.13 ± 0.23	0.012*	0.07 ± 0.12	0.019*	0.10 ± 0.17	0.040*
No	0.91 ± 0.60		0.80 ± 0.64		0.72 ± 0.51	
Combine IVI anti-VEGF						
Yes	0.63 ± 0.56	0.081	0.54 ± 0.55	0.241	0.49 ± 0.40	0.241
No	1.09 ± 0.67		0.97 ± 0.76		0.88 ± 0.66	
Operation						
Vitrectomy + TPA	0.88 ± 0.62	0.710	0.90 ± 0.75	0.568	0.88 ± 062	0.471
Gas + TPA	0.57 ± 0.52		0.61 ± 0.55		0.57 ± 0.52	
Gas + TPA + IVI anti-VEGF	0.50 ± 0.46		0.63 ± 0.77		0.50 ± 0.46	
Hypertension						
Yes	0.77 ± 0.74	0.779	0.63 ± 0.72	0.718	0.53 ± 0.45	0.659
No	0.80 ± 0.60		0.71 ± 0.64		0.67 ± 0.56	

The Wilcoxon Rank Sum test and Kruskall–Wallis test were used for comparing difference of visual improvement between groups.
anti-VEGF = vascular endothelial growth factor inhibitors; CNV = choroidal neovascularization; IVI = intravitreal injection; PDT = photodynamic therapy; RPE = retinal pigment epithelium; SD = standard deviation; TPA = tissue plasminogen activator; mo = months.
* $p < 0.05$.
[a] The Wilcoxon Rank Sum test and Kruskalle Wallis test were used for comparing difference of visual improvement between groups.

ranibizumab monotherapy in achieving complete regression of polyps.[9] Thus, combination treatment should be performed after the absorption or displacement of submacular hemorrhage to eradicate the underlying polyps, decrease the fluid in PCV, and mitigate subsequent damage from recurrent disease. However, previous study showed variant results in performing combination treatment.[3,6,20] In our study, combination with PDT was performed in three patients and intravitreal anti-VEGF injection in 13 patients. All three patients who had received PDT in our study also had further intravitreal anti-VEGF injection. The results showed that eyes treated with PDT had significant better visual prognosis at 3 months, 6 months, and 12 months.

Meyer et al[4,5] published a study using a triple intravitreal injection of TPA, gas, and Bevacizumab where other previous study reported anti-VEGF injection after hemorrhage displacement. In our study, six patients received the triple injection and five of them received further injections as needed on a monthly basis. Seven other patients had anti-VEGF injection following the removal or displacement of hemorrhage as needed. Thus, we found that performing anti-VEGF itself or the timing of performance does not differ the visual prognosis except when combined with PDT treatment.

The two subgroups of PCV are clinically and genetically different. Polypoidal CNV is thought to be associated with AMD but PCV in narrow sense is not.[10,13,14] Thus, the response to treatment and prognosis may be different. However, Yuzawa et al[15] did not mention either visual outcome or treatment effect in regards to these two different subgroups. In our study, we found that patients with polypoidal CNV had better initial BCVA than those with PCV in narrow sense. Furthermore, management of submacular hemorrhage using both surgical techniques with or without combination treatment did not show any statistically difference in visual prognosis between the two subgroups. Patients with polypoidal CNV showed deterioration but the overall mean BCVA and BCVA in those of PCV in narrow sense showed statistical improvement at 3 months, 6 months, and 12 months. This may be attributed to the small sample size of patients with polypoidal CNV. However, we can still conclude from our results that submacular hemorrhage secondary to PCV in narrow sense had better treatment response, gains in visual benefit than those due to polypoidal CNV.

Previous studies have reported variable prognosis factors for visual prognosis.[2,3,13,17,20] In our study, we found that good initial BCVA, small initial size of submacular hemorrhage and young age were statistically significant predictors for better visual prognosis. Other factors such as sex, hypertension, duration of hemorrhage, and presence of RPE detachment did not influence the outcome.

We found that small initial sizes of submacular hemorrhage not only resulted in better visual outcome but also showed statistically lower incidence of receiving a following intravitreal anti-VEGF injection. As a result, we assume that PCV cases presenting with a small initial submacular hemorrhage may have a relatively stable long-term course. However, during the follow-up period, five patients (25%) developed PCV in the fellow eye although these were found to be associated with smaller initial submacular hemorrhage sizes. Therefore, despite the better visual outcome in PCV patients with a small sized initial submacular hemorrhage, we should be aware of the possibility of developing PCV in the fellow eye.

The clinical hallmark of PCV is the presence of an orange-red nodule-like structure beneath the RPE, and is associated with an adjacent serous RPE detachment or overlying neurosensory detachment, subretinal hemorrhage, and lipid exudates.[9] Thirteen patients (65%) in our study showed an RPE detachment associated with the submacular hemorrhage lesion at the initial visit on OCT. However, RPE detachment did not show any difference in visual prognosis or in the incidence of receiving combination treatment.

Postoperative complications such as VH, retinal detachment and tear of the RPE have been reported.[5,7,8,17] PCV and massive submacular hemorrhage were risk factors for developing VH.[7,8] In our study, the only complication was VH at an incidence of 10%, which was lower than the 15% reported by Wu et al.[8] There were no risk factors found to be associated with the occurrence of VH, which also did not affect the visual prognosis.

Despite PCV having a relatively better prognosis than neovascular AMD due to its characters of less subretinal fibrovascular proliferation, slower progression of vascular abnormality, and less rapid formation of disciform scarring,[7,8,20] severe RPE atrophy is frequently observed after a long follow up period.[6,21] In our study, we found that most of our patients all had some variable degree of RPE degeneration after the resolution of the blood clot; 50% showed a formation of a disciform scar and 25% showed RPE atrophy with a mean follow-up time of 2.9 years.

In conclusion, performing combination treatment is beneficial for submacular hemorrhage in PCV eyes. Both surgical removal of hemorrhage and pneumatic displacement were effective and safe treatment options. Despite 75% of our patients having some degree of RPE degeneration, additional PDT and anti-VEGF treatment of the underlying PCV demonstrated good visual prognosis. Other predictors include initial BCVA, initial size of submacular hemorrhage, and age.

The limitation of the present study is that it is a retrospective study of consecutive eyes treated by different methods. A controlled, randomized prospective clinical trial is needed to confirm our results.

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