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RETINAL DISORDERS

The natural history of polypoidal choroidal vasculopathy: a multi-center series of untreated Asian patients

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Abstract
Purpose We aimed to evaluate the long-term natural history of polypoidal choroidal vasculopathy (PCV) in untreated patients.
Methods This is a retrospective observational case series. Patients with symptomatic PCV who did not receive any treatment for at least 12 months were included from the records of three ophthalmic clinics in Asia. The medical records and imaging data were reviewed. Visual outcomes at month 12 and at last follow-up were analyzed. The influence of demographics and presenting features on visual outcome was analyzed.
Results A total of 32 eyes (32 patients) were included in this analysis. The mean follow-up was 59.9 months (range, 18–119 months), the mean age was 65.7 years and 21 (65.6 %) patients were male. The mean presenting logMAR visual acuity was 0.79 (Standard deviation [SD] 0.49). The center of the fovea was involved by the PCV complex in 25 eyes (78.1 %). The mean greatest linear dimension (GLD) of the PCV complex was 2584 μm (SD 880). Twenty-three eyes (71.9 %) had a cluster-of-grapes configuration on indocyanine green angiography. Leakage of fluorescein angiography was present in 29 eyes (90.6 %). The mean logMAR vision deteriorated from 0.79 at baseline to 0.88 at month 12 (p=0.11), and further to 1.14 (p=0.003) at the last follow-up. The proportion of eyes that improved, remained unchanged and worsened was 21.9 %, 31.3 % and 46.9 %, respectively, at month 12; and 28.1 %, 9.4 % and 62.5 %, respectively, at last follow-up. The proportion of eyes with logMAR vision worse than 1.0 was 28.1 % at presentation, and increased to 31.3 % at month 12 and further to 53.1 % at last follow-up. Reasons for poor vision were due to retinal, subretinal or vitreous hemorrhage, and retinal pigment epithelium (RPE) atrophy and scarring. None of the presenting features were found to significantly influence visual outcome.
Conclusions Half of eyes presenting with symptomatic PCV had a relatively benign course without treatment and some even had vision improvement. However, in the remaining eyes, vision deteriorated significantly, mainly due to hemorrhage and scarring. There may be subtypes of PCV with divergent natural history.

Keywords Polypoidal choroidal vasculopathy · Natural history · Visual outcome · Untreated · Observation

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Table 1 Summary of presenting features and outcome of eyes with polypoidal choroidal vasculopathy that did not receive treatment for at least 12 months

Patient	Age	Gender	Presenting Vision (logMAR)	Reason for no initial treatment	Month 12 vision		Last visit vision		Last follow-up (month)	Outcome	Eventual treatment	Reason for Poor vision
					Vision (logMAR)	Change from baseline	Vision (logMAR)	Change from baseline				
1	65	F	1.70	patient refused	1.70	0.00	0.88	−0.82	24	improved	Month 12	NA
2	77	M	1.00	patient refused	0.52	−0.48	0.52	−0.48	45	improved	N	NA
3	64	M	1.30	patient refused	1.00	−0.30	1.00	−0.30	24	improved	N	NA
4	71	F	1.00	patient refused	0.70	−0.30	0.70	−0.30	70	improved	N	NA
5	67	F	0.52	patient refused	1.00	0.48	0.22	−0.30	65	improved	N	NA
6	75	M	0.52	patient refused	0.70	0.18	0.30	−0.22	86	improved	N	NA
7	55	M	1.30	patient refused	0.70	−0.60	1.17	−0.13	96	improved	N	NA
8	61	F	0.10	limited activity	0.00	−0.10	0.00	−0.10	18	improved	N	NA
9	68	F	1.20	patient refused	1.30	0.10	1.18	−0.02	26	improved	N	NA
10	59	M	0.60	limited activity	0.60	0.00	0.60	0.00	74	stable	N	NA
11	57	M	1.40	advanced disease	1.40	0.00	1.40	0.00	33	stable	N	RPE atrophy, persistent leakage
12	72	M	0.00	limited activity	0.00	0.00	0.00	0.00	27	stable	N	NA
13	73	F	0.20	limited activity	0.20	0.00	0.30	0.10	36	worsened	N	Persistent leakage
14	63	M	1.00	patient refused	0.70	−0.30	1.17	0.17	119	worsened	N	Recurrent bleeding
15	53	F	0.10	patient refused	0.52	0.42	0.30	0.20	45	worsened	N	RPE atrophy/ scar
16	51	M	0.40	patient refused	0.52	0.12	0.70	0.30	89	worsened	N	Recurrent bleeding
17	61	M	1.00	patient refused	1.00	0.00	1.30	0.30	84	worsened	N	Recurrent bleeding
18	70	M	0.70	patient refused	0.70	0.00	1.00	0.30	45	worsened	N	Recurrent bleeding
19	69	M	0.50	limited activity	0.30	−0.20	0.88	0.38	45	worsened	Month 18	Persistent leakage
20	70	M	0.70	patient refused	1.22	0.52	1.17	0.47	81	worsened	N	RPE atrophy/ scar
21	74	M	1.52	patient refused	1.52	0.00	2.00	0.48	97	worsened	N	RPE atrophy/ scar
22	68	M	1.30	patient refused	1.60	0.30	1.78	0.48	65	worsened	N	RPE atrophy/ scar
23	53	M	0.52	patient refused	1.00	0.48	1.08	0.56	63	worsened	N	Persistent leakage
24	69	F	1.30	patient refused	1.70	0.40	2.00	0.70	88	worsened	N	RPE atrophy/ scar
25	71	M	1.70	patient refused	2.40	0.70	2.40	0.70	24	worsened	N	RPE atrophy/ scar
26	66	M	0.70	patient refused	0.70	0.00	1.48	0.78	99	worsened	N	Recurrent bleeding

Table 1 (continued)

Patient	Age	Gender	Presenting Vision (logMAR)	Reason for no initial treatment	Month 12 vision		Last visit vision		Last follow-up (month)	Outcome	Eventual treatment	Reason for Poor vision
					Vision (logMAR)	Change from baseline	Vision (logMAR)	Change from baseline				
27	70	M	0.10	patient refused	0.15	0.05	1.00	0.90	68	worsened	N	Recurrent bleeding
28	74	M	1.00	patient refused	1.30	0.30	2.00	1.00	72	worsened	N	Recurrent bleeding
29	61	M	0.40	limited activity	0.40	0.00	1.70	1.30	36	worsened	Month 21	Recurrent bleeding
30	72	F	0.30	patient refused	0.40	0.10	1.78	1.48	24	worsened	N	RPE atrophy/ scar
31	67	F	0.52	patient refused	1.30	0.78	2.08	1.56	66	worsened	N	RPE atrophy/ scar
32	57	F	0.70	patient refused	1.00	0.30	2.40	1.70	82	worsened	N	Recurrent bleeding

PCV polypoidal choroidal vasculopathy, *M* male, *F* female, *PED* pigment epithelial detachment, *N* no, *Y* yes, *ICGA* indocyanine green angiography, *GLD* greatest linear dimension, *FA* fluorescein angiography, *RPE* retinal pigment epithelium, *NA* not applicable

Introduction

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment in the Caucasian population over 50 years of age [1, 2]. The natural history of neovascular AMD has been well described [3, 4], and clinicians are generally well positioned to counsel patients in this respect. On the contrary, the natural history of polypoidal choroidal vasculopathy (PCV), often considered a subtype of AMD, is less well studied [2, 5]. There have been reports of highly variable course in PCV. Yannuzzi first described a prolonged, relapsing and recurring course. Clinical presentation can be in the form of chronic, multiple, recurrent serosanguinous detachments of the retinal pigment epithelium (RPE) and neurosensory retina [6, 7], although long-term vision tended to be preserved and fibrous proliferation and scarring appeared less common compared to neovascular AMD. However, significant vision loss can also occur as a result of development of chronic RPE atrophy or vitreous hemorrhage [7, 8]. Other studies have described PCV as a relatively benign condition [9–12]. Uyama followed 14 untreated eyes with PCV for at least 2 years and reported that 50 % of patients remained stable and maintained vision of 20/30 or better [13]. Sho et al. compared 110 eyes with PCV and 371 eyes with neovascular AMD, and reported that eyes with PCV may manifest clinically more slowly than AMD (mean duration from symptom onset to first clinical examination, 21.2 vs. 14.8 months respectively), and that the presenting vision was significantly better in patients with PCV compared to neovascular AMD (mean Snellen decimal VA of 0.31 vs. 0.18, respectively) [14]. Yamaoka et al. followed up eyes with PCV without coexisting classic choroidal neovascularization (CNV). Despite persistent serous retinal detachment in 11 % of eyes, 89 % had stable or improved vision without treatment at 3 months, and 83 % had stable or improved vision at 12 months [11]. Spontaneous involution of polyps may occur [7, 13, 15]. Microrips of the RPE have also been reported in up to 7.1 % of eyes with PCV, although the impact on vision appeared to be limited [16].

For over a decade, verteporfin photodynamic therapy (PDT) has been used to treat PCV, with many studies reporting more favorable treatment response compared with typical AMD [17–20]. Recently, anti-vascular endothelial growth factor (anti-VEGF) therapy, alone or in combination with PDT, has been used to treat PCV. With accumulating evidence of the benefit of therapy, studies in PCV natural history are increasingly limited. In this study, we had the opportunity to follow up eyes of patients with symptomatic PCV who were not treated, mostly for financial reasons. This case series will add unique information to existing limited understanding of the natural history of PCV.

Methods and patients

This is a retrospective, non-interventional case series that included patients identified from three ophthalmic centers in Asia (Hong Kong Eye Hospital, Singapore National Eye Center and Seoul St Mary's Hospital). The study followed the principles of the Declaration of Helsinki, and approval was obtained from institutional review boards. From the Hong Kong Eye Hospital, consecutive untreated patients with PCV were identified from a retrospective review of the outcome of patients with symptomatic PCV who attended the retina clinic from January 2001 to December 2004. From the

Table 2 Summary of clinical and angiographic features in eyes with polypoidal choroidal vasculopathy (PCV) that did not receive treatment for at least 12 months

Patient		Presenting clinical Feature involving Fovea				Presenting ICGA Feature			FA leakage	Vision at last follow-up (logMAR)	
	Presenting Vision (logMAR)	Serous PED	Haem PED	Fluid	Blood	PCV complex involving fovea centre	Polyp configuration	GLD (um)			Outcome
1	1.70	Y	N	N	Y	N	large solitary	3703	Y	0.88	improved
2	1.00	N	N	Y	Y	Y	cluster	3300	Y	0.52	improved
3	1.30	N	N	Y	Y	Y	cluster	2800	Y	1.00	improved
4	1.00	N	Y	N	Y	Y	cluster	2000	Y	0.70	improved
5	0.52	Y	N	Y	N	N	cluster	2100	Y	0.22	improved
6	0.52	N	N	N	Y	Y	cluster	1700	Y	0.30	improved
7	1.30	Y	N	Y	N	Y	cluster	2900	Y	1.17	improved
8	0.10	N	N	N	N	N	cluster	2933	Y	0.00	improved
9	1.20	Y	Y	N	Y	N	cluster	2300	Y	1.18	improved
10	0.60	N	N	N	N	Y	large solitary	1872	Y	0.60	stable
11	1.40	Y	N	Y	Y	Y	cluster	2030	Y	1.40	stable
12	0.00	N	N	Y	N	Y	large solitary	2127	Y	0.00	stable
13	0.20	Y	N	N	N	Y	cluster	1800	N	0.30	worsened
14	1.00	Y	N	N	N	Y	cluster	3300	Y	1.17	worsened
15	0.10	N	Y	N	N	Y	cluster	2500	Y	0.30	worsened
16	0.40	N	N	N	Y	Y	large solitary	2800	Y	0.70	worsened
17	1.00	N	N	N	Y	Y	cluster	3400	Y	1.30	worsened
18	0.70	Y	N	N	N	Y	cluster	3200	Y	1.00	worsened
19	0.50	N	N	N	N	N	large solitary	1982	N	0.88	worsened
20	0.70	Y	N	N	Y	Y	cluster	1300	Y	1.17	worsened
21	1.52	N	Y	N	Y	Y	cluster	1600	Y	2.00	worsened
22	1.30	N	N	N	Y	Y	large solitary	2300	Y	1.78	worsened
23	0.52	Y	N	N	N	Y	cluster	3900	Y	1.08	worsened
24	1.30	Y	Y	N	N	N	cluster	2700	Y	2.00	worsened
25	1.70	N	N	Y	Y	Y	cluster	5664	Y	2.40	worsened
26	0.70	Y	N	N	Y	Y	cluster	1900	Y	1.48	worsened
27	0.10	Y	Y	N	Y	Y	cluster	2400	Y	1.00	worsened
28	1.00	N	N	Y	N	Y	large solitary	2100	Y	2.00	worsened
29	0.40	N	N	N	N	N	large solitary	3376	N	1.70	worsened
30	0.30	N	N	Y	Y	Y	cluster	2300	Y	1.78	worsened
31	0.52	N	N	N	Y	Y	large solitary	1400	Y	2.08	worsened
32	0.70	Y	N	Y	Y	Y	cluster	3000	Y	2.40	worsened

PCV polypoidal choroidal vasculopathy, *M* male, *F* female, *PED* pigment epithelial detachment, *N* no, *Y* yes, *ICGA* indocyanine green angiography, *GLD* greatest linear dimension, *FA* fluorescein angiography, *RPE* retinal pigment epithelium, *NA* not applicable

Singapore National Eye Centre, untreated patients with symptomatic PCV were identified from the ongoing Asian AMD Phenotyping study. This is a prospective observational clinical study of Asian patients with new onset AMD or PCV in Singapore. Recruitment started on 1 March 2010 and is still ongoing [21]. Informed consent forms were signed by all participants. Due to the prospective nature, only patients who agreed to participate in the study were included, thus representing a non-consecutive series. From the Seoul St Mary's Hospital, consecutive patients were identified from a retrospective review of the outcome of patients with symptomatic PCV who attended the retina clinic from January 2010 to December 2012.

All patients had symptomatic PCV, defined as any visual loss and/or metamorphopsia on clinical presentation.

From each center, fundus photography, fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed at presentation. The diagnosis of PCV was

Table 3 Baseline characteristics of eyes with polypoidal choroidal vasculopathy that did not receive treatment for at least 12 months, further divided according to visual outcome at last follow-up

	Overall (n=32)	Worsened (n=20)	Stable or improved (n=12)	p
Age, Mean (SD)	65.7 (7.1)	65.6 (7.3)	65.8 (7.2)	0.93
Gender, Male (n, %)	21 (65.6 %)	14 (70.0 %)	7 (58.3 %)	0.38
Presenting visual acuity, LogMAR Mean (SD)	0.79 (0.49)	0.73 (0.46)	0.89 (0.53)	0.40
Month 12 visual acuity, LogMAR, Mean (SD)	0.88 (0.56)	0.93 (0.59)	0.80 (0.52)	0.53
Change visual acuity at Month 12, LogMAR, Mean (SD)	+0.09 (0.32)	+0.20 (0.29)	−0.09 (0.30)	0.012
Month 24 visual acuity, LogMAR, Mean (SD), n=31	0.87 (0.56)	NA	NA	
Change visual acuity at Month 24, LogMAR, Mean (SD), n=31	+0.05 (0.40)	NA	NA	
Month 36 visual acuity, LogMAR, Mean (SD), n=24	1.20 (0.61)	NA	NA	
Change visual acuity at Month 36, LogMAR, Mean (SD), n=24	+0.46 (0.49)	NA	NA	
Month 60 visual acuity, LogMAR, Mean (SD), n=18	2.10 (0.20)	NA	NA	
Change visual acuity at Month 60, LogMAR, Mean (SD), n=18	+0.97 (0.53)	NA	NA	
Last visit visual acuity, LogMAR, Mean (SD)	1.14 (0.68)	1.43 (0.63)	0.66 (0.47)	0.001
Change in visual acuity at last visit, LogMAR, Mean (SD)	+0.35 (0.61)	+0.69 (0.49)	−0.22 (0.24)	< 0.001
Follow-up duration in month, Mean (SD)	59.9 (27.9)	66.4 (26.5)	49.0 (27.6)	0.087
Proportion with vision:	Baseline M12 M24	M36	M60	Final
≤ 0.3 LogMAR	15.6 % 12.5 % 12.9 %	8.3 %	5.6 %	9.4 %
> 1.0 LogMAR	28.1 % 31.3 % 25.8 %	62.5 %	44.4 %	53.1 %
Lesion Characteristics at Baseline				
Greatest linear dimension, μm Mean (SD)	2584 (880)	2646 (1012)	2480 (630)	0.614
Serous PED involving fovea (n, %)	14 (43.8 %)	9 (45.0 %)	5 (41.7 %)	0.574
Hemorrhagic PED involving fovea (n, %)	6 (18.8 %)	4 (20.0 %)	2 (16.8 %)	0.601
Fluid at fovea (n, %)	9 (28.1 %)	4 (20.0 %)	5 (41.7 %)	0.180
Blood at fovea (n, %)	18 (56.3 %)	11 (55.0 %)	7 (53.3 %)	0.574
Cluster of polyps configuration (n,%)	23 (71.9 %)	13 (65.0 %)	9 (75.0 %)	1.00
PCV complex involving fovea (n,%)	25 (78.1 %)	17 (85.0 %)	8 (66.7 %)	0.218
Leakage on fluorescein angiography (n,%)	29 (90.6 %)	17 (85.0 %)	12 (100.0 %)	0.230
Reason for Poor outcome	NA	Persistent Leak (15 %) RPE scar (40 %) Hemorrhage (45 %)	NA	NA

P value compare between worsened group and stable or improved group, by Fisher exact test or student *t* test, as appropriate

confirmed on ICGA by demonstration of typical polypoidal lesions. For all patients, the risk versus benefit of observation versus treatment options available at the time (including PDT, anti-VEGF and/ or focal laser photocoagulation) was explained. For this series, patients were monitored every 3 to 6 months after they declined to have treatment at presentation. Only patients with a minimum follow-up duration of at least 12 months were included in this analysis.

Inclusion criteria for the current analysis included patients: 1) with symptomatic PCV defined by ICGA at baseline, defined by one or more focal vascular dilatations in the inner choroidal circulation; 2) who did not receive any treatment for PCV within 12 months of presentation; and 3) who had at least 12 months follow-up data.

The medical records and imaging data of all identified patients were reviewed. Baseline demographic, clinical and imaging features were analyzed. Change in vision at month 12, and at latest follow-up, and reason for visual loss were noted. Snellen visual acuity was converted to logarithm of minimal angle of resolution (logMAR) unit for analysis. Presenting features, including presence or absence of serous pigment epithelium (PED), hemorrhagic PED, blood and subretinal fluid involving the fovea were graded using fundus photograph and FA by a single investigator at each site. Greatest linear dimension (GLD) was measured with Imagenet software (Topcon, Tokyo, Japan) or HRA software (Heidelberg Retina Angiograph, Heidelberg Engineering, Heidelberg, Germany) based on ICGA. Polyp configuration (single solitary versus

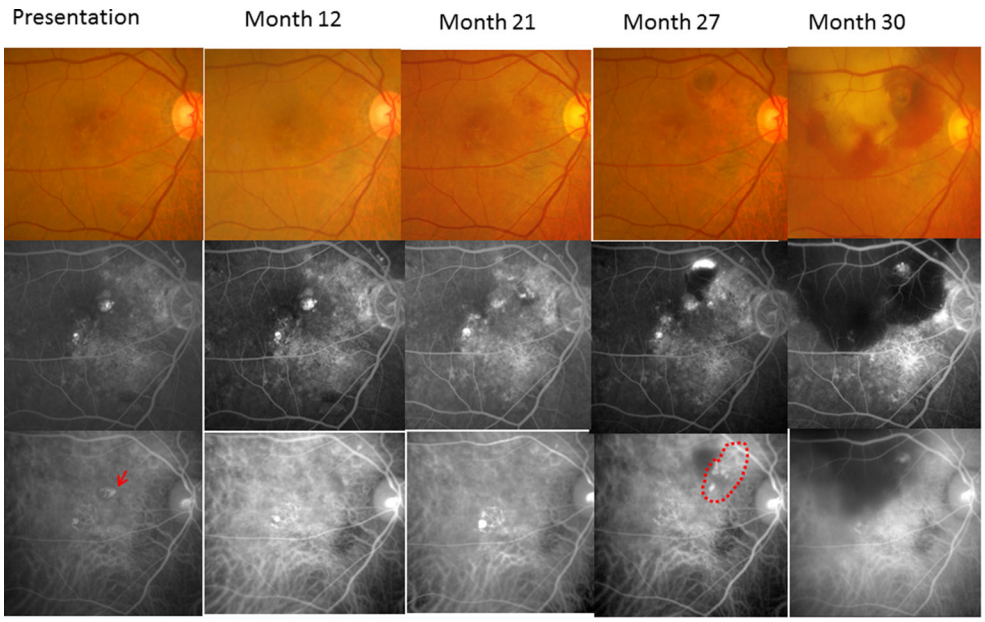

Fig. 1 Example of natural progression of an eye with a large solitary polyp (patient 29) from presentation through to month 21, and subsequent worsening through to month 30, despite treatment commencement at month 21. (*Top row* – Color photograph; *Middle row* – Fluorescein angiography, *Bottom row* – Indocyanine green angiography). At presentation, two polyps can be seen on ICGA, with corresponding orange nodules on color fundus photograph. There was little leakage on FA and vision was 0.40. No treatment was given. At month 12, one of the polyps appear to have resolved (indicated by red arrow at presentation), and the corresponding orange nodule on color photo was also not apparent anymore. Vision was stable at 0.40. At Month 21 however, subretinal fluid developed, with a drop in vision to 0.56. Patient received one ranibizumab injection followed by two further bevacizumab injections. Repeat ICGA at Month 27 showed improvement of the subfoveal cluster of polyps and no further subretinal fluid at the fovea, vision of 0.70. A new cluster of extrafoveal polyps (*red dotted line*), which was not previously present, was noted. No treatment was given between Month 27 and Month 30. A new subretinal hemorrhage developed at Month 30. The patient underwent focal laser and intravitreal bevacizumab. However, final visual acuity at Month 36 was finger counting only

cluster of small polyps) was also graded using ICGA images from presentation.

For statistical analyses, Fisher's exact test and two-sample *t*-test were performed. A p value of 0.05 or less was considered as statistically significant.

Results

Patient characteristics

A total of 32 eyes from 32 patients who met the inclusion criteria were included in this analysis. These included 23 eyes of 23 patients from the Hong Kong Eye Hospital, identified from 75 PCV patients reviewed, and seven eyes of seven patients from the Singapore National Eye Centre, identified from a cohort of 144 PCV patients, as well as two eyes of two patients from the Seoul St Mary's Hospital. The clinical characteristics of these 32 eyes are summarized in Table 1 and Table 2. The most common reason for non-treatment was patient refusal, mostly due to financial constraint (25 patients, 78.1 %). In the remaining patients, the lesion was felt to be of limited activity in six patients, but was too advanced to benefit from treatment in one patient. All patients had at least 12 months of follow-up. The mean follow-up was 59.9 months (range, 18–119 months). Three patients (Patient 1, 19 and 29) eventually received treatment after 12 months, due to progression of the condition.

Presenting features (Table 1 and Table 2)

The mean age at presentation was 65.7 years and 21 (65.6 %) patients were male. Thirteen patients (40.6 %) had a history of hypertension. The mean presenting logMAR visual acuity was 0.79 (SD 0.49). Five eyes (15.6 %) had presenting logMAR visual acuity of ≤ 0.3, and nine patients (28.1 %) had presenting vision worse than 1.0. PCV was confirmed on ICGA in all cases, and the center of the fovea was involved by the PCV complex in 25 eyes (78.1 %). The mean GLD of the PCV complex was 2584 μm (SD 880). Activity was assessed by the presence of leakage in FA (29 eyes, 90.6 %), or the presence of any of the following four features: presence of serous PED (14 eyes, 43.8 %), presence of hemorrhagic PED (six eyes, 18.8 %), presence of subretinal fluid (nine eyes, 28.1 %) or presence of subfoveal blood (18 eyes, 56.3 %). At least one of these four features was present in 27 eyes (84.4 %). Twenty three eyes (71.9 %) had a cluster-of-grapes configuration on ICGA.

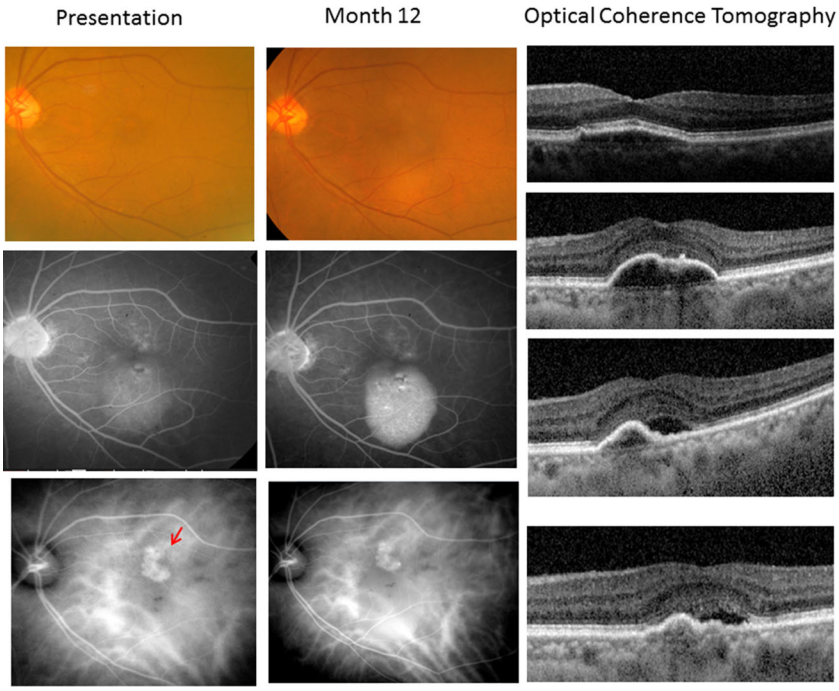

Fig. 2 Example of natural history of an eye (patient 13) with clustered polypoidal choroidal vasculopathy (PCV) that showed gradual worsening and persistent exudation from presentation through to month 36. Image at baseline (*Left column*, *top* – Color photo; *Middle* – Fluorescein angiography; *Bottom* – Indocyanine green angiography) showed mild pooling without significant leakage on FA and cluster of polyps (*red arrow*). At month 12 (*Central column*), the pigment epithelial detachment has enlarged on fluorescein angiography. Optical coherence tomography (*Right column from top* – baseline, month 12, month 24 and month 36) showed shallow pigment epithelial detachment at baseline, which increased in height at month 12, and subsequent development of subretinal fluid at month 24 persisting to month 36

Visual outcome (Table 1)

The mean logMAR visual acuity deteriorated from 0.79 at baseline to 0.88 at month 12 (n=32), 0.87 at Month 24 (n=31), 1.01 at Month 36 (n=24) and 1.21 at Month 60 (n=18). The mean visual acuity was 1.14 at the last follow-up. The percentage of eyes that improved was 21.9 % at month 12, 29.0 % at month 24, 20.8 % at month 24 and 22.2 % at month 60. The percentage of eyes that worsened was 46.8 % at month 12, 51.6 % at month 24, 54.2 % at month 36 and 55.6 % at month 60. (Table 3). The proportion of eyes with visual acuity better than 0.3 decreased from 15.6 % at presentation, to 12.5 % at month 12, 12.9 % at month 24, 8.3 % at month 36 and 5.6 % at month 60. The proportion of eyes with vision worse than 1.0 increased from 28.1 % at presentation, to 31.3 % at month 12, 25.8 % at month 24, 62.5 % at month 36 and 44.4 % at month 60. (Table 1). Among the 20 eyes that worsened (defined as any drop in BCVA at last follow-up), the most common reasons were due to hemorrhage, retinal pigment epithelium atrophy and persistent leakage. (Figs. 1 and 2). If we defined worsening as a drop in BCVA by two lines (0.2 LogMAR units), 18 of the 20 eyes (56.3 % of the whole cohort) would have been categorized as having vision worsening at the last follow-up.

We further compared the presenting features between the eyes that worsened and the eyes that remained stable or improved. However, none of the demographic factors or presenting features studied were found to be significantly different between the two groups (Table 3).

Discussion

The natural history of PCV is often thought to be more benign than neovascular AMD [13]. However, PCV tends to have a relapsing and recurring pattern. Therefore, significant visual loss may occur with longer follow-up. There have been few studies reporting the natural history of untreated PCV, and these have been summarized in Table 4. As treatment modalities such as PDT and anti-VEGF therapy become increasingly available, the opportunity to study the natural history of untreated PCV will become increasingly limited. Uyama followed 14 eyes with PCV for 2 years and reported that 50 % remained stable and maintained vision of 20/30 or better [13]. However, there have been other series that have reported significantly higher proportion of eyes with visual loss [22, 23] (Table 3). In our current series, we followed 32 eyes with symptomatic PCV that remained untreated for at least 12 months. We found that half of these eyes had a relatively benign course without treatment and some even had vision improvement. However, in the remaining eyes, vision

Table 4 Summary of reported outcome of eyes with polypoidal choroidal vasculopathy that did not receive treatment

Study	Untreated eyes	Mean follow-up (months)	Presenting vision	Presenting features	Angiographic feature	Outcome	Reason for poor outcome
Yannuzzi et al. [7]	65		–	Marked variability with respect to size, location and course		Many patients demonstrated chronic multiple recurrent serosanguineous detachments of the RPE and neurosensory retina with long-term preservation of good vision Some develop chronic atrophy and cystic degeneration of the fovea with severe vision loss Some had vitreous hemorrhage, secondary CNV with disciform scarring and profound loss of central vision	
Moorthy et al. [10]	5	43.2	0.29	Elevated, orange subretinal lesions with overlying subretinal fluid Hemorrhagic detachment of RPE Large subretinal hemorrhage, vitreous hemorrhage		3 out of 5 patients had spontaneous resolved lesions, including large subretinal hemorrhage, with good vision (20/20 to 20/50) 1 patient had hand motions vision due to dense vitreous hemorrhage (1 patient did not return)	
Uyama et al. [30]	18	20	–	Serous RD, subretinal hemorrhages, large serous PEDs, hemorrhagic PEDs, diffuse RPE degeneration Macular lesions measured 2–3 disc diameter		Stable- 66.7 %	Serous RD – 16.7 % Subretinal hemorrhage – 11.1 % Vitreous hemorrhage – 11.1 % Disciform scar – 15.6 %
Sho et al. [14]	110	21.9	0.50	Exudative – 59 % Hemorrhagic – 30 % RPE atrophy – 10 %	Cluster subtype – 9 % Associated with classic CNV – 9 %	Severe visual loss – 35 % (by at least 0.2)	Persistent serous RD Subretinal fibrosis Massive hemorrhage
Uyama et al. [13]	14	39.9	0.31	Exudative 10/14 Hemorrhagic 4/14	Large solitary 10/14 Polypoidal CNV 4/14 Cluster subtype 25 %	Final VA – 0.50 Maintained 20/30 or better – 50 % Deteriorated to 20/100 or worse – 43 %	RPE degeneration Persistent leak Hemorrhage Only 2/12 eyes with good presenting VA did poorly
Kwok et al. [22]	13	0.65	28.2	Subretinal hemorrhage, retinal exudation, hemorrhagic PED, serous PED		Final VA – 1.14 Improve – 7.7 % Stable – 23.1 % Worsened – 69.2 % (by ≥ 2 Snellen lines)	Disciform scarring Exudative maculopathy
Bessho et al. [12]	42	12	0.48 (SD 4.0)	Hemorrhagic 62 %	Clustered pattern 50 % Non-clustered pattern 40 %	Final VA 0.75 (SD 5.7) Improved – 24 % Worsened – 48 % (by at least 0.2)	Sudden bleed 33 %
Yamaoka et al. [11]	112	3	0.41	Serous RD – 44 % Serous PED – 57 % Hard exudates – 14 %	No Classic CNV	Improved – 17 % Stable – 72 % Worsened – 11 %	Persistent exudation

Table 4 (continued)

Study	Untreated eyes	Mean follow-up (months)	Presenting vision	Presenting features	Angiographic feature	Outcome	Reason for poor outcome
				Hemorrhagic PED – 8 %		(by at least 0.2) Improved- 19 % Stable – 64 % Worsened – 16 %	
	Subgroup of 67 patients with 12 months follow-up					(by at least 0.2)	
Okubo et al. [9]	13	80	0.28 (SD 0.26)	Group 1: (n=9) Reddish-orange nodules and detachment of RPE +/− RD Group 2: (n=4) Reddish-orange nodules alone +/− subretinal hemorrhage	Group 1: a number of polypoidal structures that varied from 1 to several +/− vascular networks Group 2: 1 or 2 polypoidal structures focally without vascular networks	Final VA 0.62 (SD 0.72) Group 1: Improved – 1/9 Stable – 4/9 Worsened – 4/9 Group 2: Stable- 100 %	RPE atrophy Chorioretinal atrophy Macular edema
Pauleikoff et al. [23]	14	9.1	0.48	PED associated with PCV	PED enlarged in diameter and volume	Final VA- 1.48 11 eyes (78.6 %) lost <3 lines	Persistent PED – 53.4 % RPE atrophy- 10.9 % Disciform scar – 23.8 % RPE tear – 11.9 %

deteriorated significantly, and 56 % of eyes had worsening of vision by two or more lines. As a group, the mean visual acuity of the whole group deteriorated significantly from 0.79 at presentation to 1.14 at the last follow-up. The proportion of eyes with vision worse than 1.0 increased from 28.1 % at presentation to 31.3 % at month 12, and further to 53.1 % at final visit. These data suggest there may be subtypes of PCV with divergent natural history.

One of the challenges in understanding the natural history of PCV is that this condition appears heterogeneous. Configuration of polyps on ICGA has been described as one of the significant factors in predicting the clinical course. A "cluster-of-grapes" configuration of polyps, in particular, has been described as usually following a more aggressive course with or without treatment [13, 14, 24]. The prevalence of this subtype of PCV has been reported to range from 9 to 67 % [12–14, 25]. However, the criteria for "clustered polyps" were somewhat subjective, and there were no widely recognized criteria in terms of morphology and number of polyps. In the current series, a high proportion (76.7 %) of eyes exhibited this configuration at presentation, which may explain the large proportion of eyes with deterioration. Bessho et al. followed 42 eyes with PCV over 12 months and reported that mean visual acuity was maintained in eyes showing "non-clustered" PCV, while eyes with "clustered" PCV experienced significant deterioration during the same period [12]. Okubo divided eyes with PCV according to the ICGA features and reported that all eyes with one to two polypoidal structures focally without branching vascular network remained stable, as opposed to eyes which exhibited a number of polypoidal structures associated with vascular networks [9]. Yuzawa et al. performed detailed examination of the internal angio-architecture of polypoidal complex based on high-speed ICGA, and suggested there may be two types of PCV: PCV with inner choroidal vessel abnormalities in the strict sense and polypoidal CNV in which neovascular process may accompany the presence of polyps. In the second type, the lesion tended to expand rapidly under the RPE, developing polypoidal lesions at the vessel termini [26]. These differences may further explain the variations in clinical features and prognosis. There appears to be a consistent subgroup of PCV, particularly those with non-clustered configuration, one to two polyps without vascular network and smaller GLD, or the 'PCV in the strict sense' that have a relatively benign natural history, and may even improve spontaneously without treatment.

With the availability of video ICGA, it is now possible to study the presence of pulsatility within polypoidal lesions [26–28]. Byeon et al. reported that pulsatility can be seen in 22.2 % of eyes with PCV, and suggested that extensive hemorrhage may be associated more closely with pulsating than non-pulsating PCV [27]. The presence of pulsatile polyp is also of diagnostic significance, as pulsatile polyp is also one of the diagnostic criteria as used in the EVEREST study

evaluating the use of ranibizumab and PDT in the treatment of PCV [29].

In terms of clinical presentation, many investigators have broadly divided PCV eyes into a predominantly exudative pattern versus a hemorrhagic pattern. The distribution of these two patterns varies between series [14, 22, 30]. In the exudative pattern, serous RPE or retinal detachment and lipid deposits may continue for a long time in a stable condition, followed by eventual degeneration and atrophy of the RPE and deterioration in vision [13]. In the hemorrhagic pattern, hemorrhagic PED and/or submacular hemorrhage, sometimes acute, can occur, leading to sudden visual deterioration. Massive retinal hemorrhage may even lead to breakthrough vitreous hemorrhage. The hemorrhage may resolve spontaneously, but repeated recurrences can occur, ultimately leading to degeneration of the RPE and outer retina and visual loss. Eyes with PCV may also alternate the pattern of manifestation during follow-up. In the current series, there was a high proportion of eyes with predominantly hemorrhagic pattern at presentation, and hemorrhage was the most common reason for progressive visual loss.

Other factors that have been suggested to influence the natural history of untreated PCV also include initial vision, lesion size and disease duration. Eyes with better initial vision tended to maintain their vision at 1 year [11] and 2 years [13]. Eyes with smaller lesion and shorter duration showed a slower rate of visual decline during observation than eyes with la\rger lesions and longer history [31]. Furthermore, many eyes with smaller lesion did not vary over time, whereas prolonged exudation and fibrotic scar formation were more commonly seen in eyes with larger lesion and longer duration. Unfortunately, based on the current study design, we have not been able to include disease duration in our analysis, as this information was obtained from subjective patient recall and was also not uniformly recorded in the case notes. Presence of co-existing type II CNV has also been described in a small proportion of patients with PCV, and is associated with worse prognosis [11, 32–34].

The strengths of our current study include a relatively large number of untreated PCV eyes that were followed for a prolonged period from three Asian centers. Limitations include the fact that patients who remained on follow-up might be biased, and patients who defaulted both treatment and follow-up might have a different clinical course. Patients who refused initial treatment due to financial reason are also much less likely to have follow-up examinations unless there is significant worsening. For the same reason, the analysis of risk factors for worsening using last follow-up should also be interpreted with caution. In order to mitigate this limitation, we have included the visual outcome at various interim time points where available. Optical coherence tomography data were not available in some patients at presentation, and therefore were not included as a factor for analysis. The inability to demonstrate any of the studied presenting factors in influencing visual outcome was likely due to small sample size. In addition, all eyes in this series had symptomatic PCV, and we are planning a prospective study of asymptomatic fellow eyes requiring a much larger sample size.

In summary, we report the natural history in a series of 32 untreated eyes with symptomatic PCV in Asian patients. Half of the eyes had a relatively benign course and some were even able to have vision improvement without treatment. However, in the remaining eyes, vision deteriorated significantly, mainly due to hemorrhage and scarring. The findings suggest that there might be two subtypes of PCV with divergent natural history. On-going randomized clinical trials with larger sample sizes will guide the best approach to manage patients with PCV.

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