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Different imaging characteristics between unilateral and bilateral polypoidal choroidal vasculopathy

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ABSTRACT

Purpose: To investigate the different imaging characteristics between unilateral and bilateral polypoidal choroidal vasculopathy (PCV) cases, based on confocal scanning laser ophthalmoscope assessment.

Methods: For this retrospective case series study, diagnostic indocyanine green angiography (ICGA) and spectral domain optical coherence tomography (SD-OCT) were performed to assess the eligible PCV eyes.

Results: Among the 53 patients at baseline, 14 showed bilateral PCV lesions, including two cases of branching vessel network (BVN) without leakage. Concerning the subfoveal choroidal thickness (SFCT), unilateral PCV eyes (326 [155–547] μm) were statistically comparable to their fellow eyes (330 [163–477] μm) ($p = 0.257$). However, the SFCT (228[141–273] μm) from the bilateral PCV group was significantly lower compared with both the PCV ($p = 0.002$) and fellow eyes ($p < 0.001$) from the unilateral group. Moreover, ICGA related hyperfluorescent spots were shown to have a significant positive correlation with SFCT in the unilateral PCV eyes and their fellow eyes, other than bilateral PCV cases. In addition, the drusens tended to prevail in the fellow eyes of the unilateral PCV group (46.2%), compared with bilateral cases.

Conclusions: Our results indicate that SFCT, ICGA related hyperfluorescent spots, and drusen were the three main imaging characteristic differences between unilateral and bilateral PCV cases.

1. Introduction

Polypoidal choroidal vasculopathy (PCV), which was initially described by Yannuzzi, et al., is a choroidal vascular abnormality characterized by branching choroidal vessels with polyp-like terminal aneurysmal dilations [1]. Moreover, PCV has a higher prevalence in individuals with darker pigmented skin [2]. Characteristic findings comprise orange-red lesions detected by fundus examination or characteristic polypoidal lesions detected with indocyanine green angiography (ICGA) [3]. Histologically, two main abnormalities found with PCV include both the degenerated retinal pigment epithelium (RPE)-Bruch's membrane choriocapillaris complex and an inner choroid with tortuous and degenerated arterioles [4]. Additionally, cluster of grape-like polypoidal lesions may induce bleeding and leakage with a high risk of severe visual loss [5].

In clinical practice, bilateral PCV cases are occasionally found. The risk of developing PCV in the fellow unaffected eye should increase clinical prevention and intervention efforts. Giovannini, et al., stated that PCV is not a bilateral disease, and 78.9% of polypoidal lesions were unilateral, which was in accordance with observations made in a Japanese population [2]. However, some authors have suggested that PCV is a bilateral disease, with the majority of patients developing similar lesions in the fellow eye, and the bilateral occurrence of PCV has been reported to be 24.1% (Korean), 18.4% (Japanese), 10% (Japanese), 24.7% (Chinese), and 25% (Caucasian) [6]. Additionally, cumulative bilateralilty of PCV has been proven to appear with increasing age. In unilaterally affected Japanese patients, typical age-related macular degeneration (AMD) and PCV showed very similar probabilities for the fellow eye to become affected, with a cumulative incidence of 3.2%, 11.1%, and 11.1% at one, three, and five years, respectively [7]. Additionally, the mean age of patients with bilateral PCV was 67.9 years, which did not differ significantly from patients with unilateral PCV [6].

On the other hand, PCV eyes with choroidal vascular hyperpermeability demonstrated greater subfoveal choroidal thickness (SFCT) than those without choroidal vascular hyperpermeability [8]. In our previous analysis, there was no difference between SFCT in PCV eyes (243 [106–417] μm) and fellow eyes (248 [100–399] μm) [9], which may indicate a symmetrical choroidal anatomy in PCV patients. In addition, RPE atrophy has been shown to be prevalent in fellow eyes of patients who developed PCV, as have inner choroidal vascular abnormalities of the vascular network and polypoidal formation in eyes before the

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clinical manifestations of exudative change [7]. In addition, Hwang, et al. [10], reported that late geographic hyperfluorescence was noted in 27.3% of fellow eyes in 11 PCV cases that underwent bilateral indocyanine green angiography at diagnosis. However, there no research has yet focused on the imaging characteristics of both unilateral and bilateral PCV cases.

A relatively high incidence of pathological findings in the fellow eye and bilateral involvement suggest the need for bilateral examinations [10]. In this retrospective study, we examined PCV patients, in order to investigate the similar and different imaging characteristics between unilateral and bilateral PCV cases, using multimodal imaging, based on confocal scanning laser ophthalmoscope assessments.

2. Methods

2.1. Patients and imaging acquisition

This retrospective study included consecutive patients who were diagnosed with definitive PCV lesions from September 2012 to June 2018 according to the Japanese Study Group guidelines published in 2005 [11], based on the characteristic polypoidal structures at the border of the choroidal branching vascular networks (BVN), visualized with ICGA [12], and the presence of an orange nodule in the fundus. Patients with diabetic retinopathy, retinal vein occlusion, or central serous chorioretinopathy in either eye were excluded from this study. All patients underwent best-corrected visual acuity and fundus examinations with dilated pupils. Dynamic ICGA (excitation, 787 nm; emission, 800 nm; field-of-view, 30° × 30°; image resolution, 768 × 768 pixels) and fundus fluorescein angiography (FFA, excitation, 488 nm; emission, 500 nm; field-of-view, 30° × 30°; image resolution, 768 × 768 pixels) were performed simultaneously to detect polyps and BVN using a multi-modality imaging system (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) for PCV diagnosis. The angiography images were captured and viewed in stereo. Spectral-domain optical coherence tomography (SD-OCT, Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) with automatic real-time tracking was used to achieve data acquisition rates of up to 40,000 axial scans/second. Raster scans (30°) with an average of 22 scan lines (range 16–39) were performed in the automatic real time mode through the polyps and fovea (Fig. 1). The angiographic images were read with co-location SD-OCT. A total of 35 of 53 PCV cases finally received photodynamic therapy. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of China Medical University. Informed consent was obtained from all subjects.

2.2. Main measurements

For both PCV and fellow eyes, SFCT was measured at baseline using the Heidelberg Eye Explorer software (version 1·5·12·0, Heidelberg Engineering). The angiographic characteristics during the early and middle stages of ICGA, including hyperfluorescent spots [13] and BVN [14], were investigated bilaterally; double-layer sign, RPE detachment (RPED), and drusen were recorded with SD-OCT.

2.3. Statistical analyses

Statistical analyses were performed using SPSS (version 19.0; IBM Inc., Chicago, IL, USA). The data are expressed as medians (range). The difference in SFCT was analyzed by Wilcoxon matched-pair signed-rank tests. The differences and relationships of both angiographic and OCT features were separately analyzed by Pearson's chi-square test and Spearman's correlation. A P value < 0.05 was considered statistically significant.

3. Results

3.1. General information

According to the ICGA results, 53 PCV patients were enrolled, including 24 men and 29 women (mean age, 64 [range, 47–75] years). In addition, 14 out of the total 53 patients (26.4%) had bilateral PCV lesions, including two BVN cases without any leakage, and 18.9% of PCV polyps were directly detected by OCT (Fig. 2).

3.2. OCT features

In the unilateral PCV group, the SFCT in PCV eyes (326 [155–547] μm) appeared to be statistically similar to the SFCT in the fellow eyes (330 [163–477] μm) ($Z = 1.132$, $p = 0.257$). However, the SFCT in the bilateral PCV group (228[141–273] μm) was significantly lower than in both the PCV group ($Z = 3.073$, $p = 0.002$) and in fellow eyes ($Z = 3.932$, $p < 0.001$) from the unilateral group (Fig. 3).

The rate of double-layer sign and RPED on OCT in the fellow eyes of the unilateral PCV group (15.4%, 30.8%) was significantly lower than that in the unilateral PCV (89.7%, $X^2 = 40.311$, $p < 0.001$; 89.8%, $X^2 = 25.911$, $p < 0.001$) and bilateral PCV eyes (82.1%, $X^2 = 29.589$, $p < 0.001$; 71.4%, $X^2 = 10.799$, $p = 0.001$). However, no differences were found between the latter two (double-layer sign: $X^2 = 0.288$, $p = 0.592$; RPED: $X^2 = 2.577$, $p = 0.108$).

Moreover, there was a positive relationship between SFCT and double-layer sign in the fellow eyes of the unilateral PCV group ($R = 0.342$, $p = 0.033$). In addition, there was a strong positive relationship between RPED and BVN in the bilateral PCV eyes ($R = 0.826$, $p < 0.001$).

On the contrary, drusen tended to prevail in the fellow eyes of the unilateral PCV group (46.2%), compared with the unilateral PCV eyes (15.4%, $X^2 = 8.667$, $p = 0.003$). No drusen were detected in bilateral PCV eyes.

3.3. Angiographic characteristics

The detectable rate of BVN, as evaluated by ICGA, in unilateral PCV eyes (92.3%) was similar to that of bilateral PCV eyes (71.4%, $X^2 = 3.768$, $p = 0.052$).

Moreover, there was no significant difference in the proportion of eyes with hyperfluorescent spots during ICGA between PCV eyes in the unilateral PCV group (69.2%) and those in the bilateral PCV group (60.7%) ($X^2 = 0.524$, $p = 0.469$). Nevertheless, the proportion of eyes with hyperfluorescent spots in the fellow eyes of the unilateral PCV group (23.1%) was lower, compared with unilateral PCV ($X^2 = 16.714$, $p < 0.001$) and bilateral PCV eyes ($X^2 = 9.723$, $p = 0.002$) (Fig. 4).

In the unilateral PCV eyes, ICGA related hyperfluorescent spots were shown to have significant positive correlations with both SFCT ($R = 0.433$, $p = 0.006$) and BVN ($R = 0.401$, $p = 0.011$). Similarly, for the fellow eyes, ICGA hyperfluorescent spots were positively related with SFCT ($R = 0.342$, $p = 0.033$), RPED ($R = 0.426$, $p = 0.007$), and double-layer sign on OCT ($R = 0.778$, $p < 0.001$). Bilateral PCV eyes showed a positive relationship between hyperfluorescent spots and double-layer sign on OCT ($R = 0.580$, $p = 0.001$).

4. Case reports

4.1. Case 1

A 59-year-old woman had been complaining of blurred vision in her left eye for one year. ICGA of her left eye showed BVN with polyps in the macula and blocked fluorescence due to subretinal hemorrhage in the early and middle phases. In particular, there were several clusters of hyperfluorescent spots in the middle stage of ICGA. Interestingly, ICGA of her right eye similarly presented BVN and hyperfluorescent spots

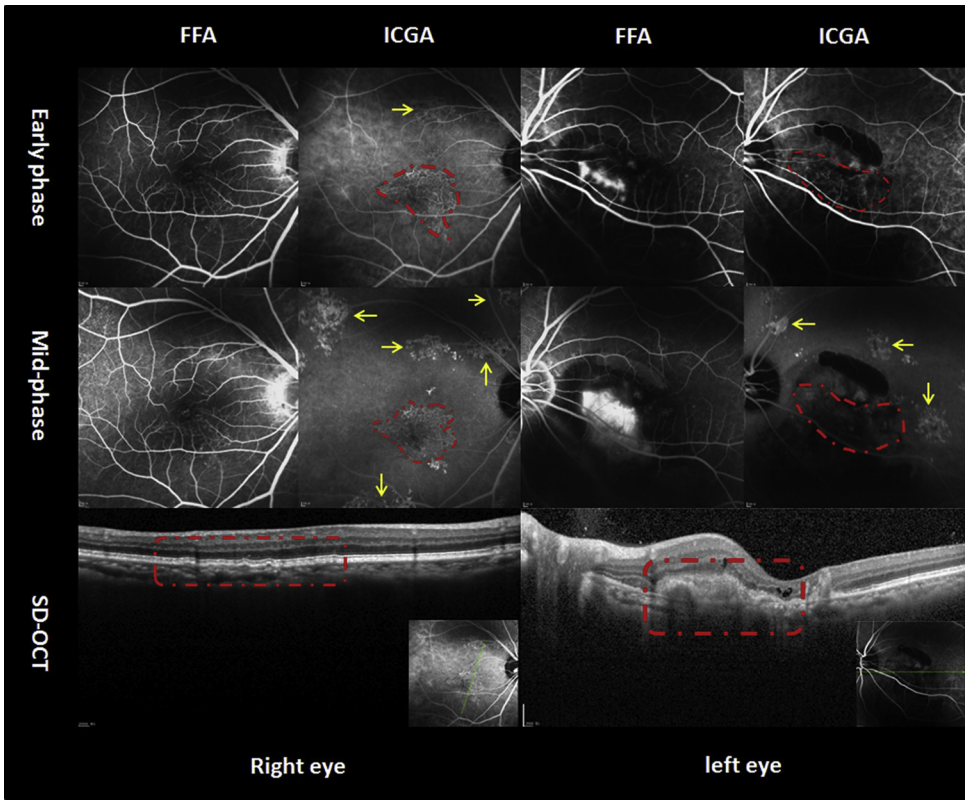

Fig. 1. Examinations of PCV patients and the illustration of Case 1. The main examinations included bilateral FFA, ICGA (both early and middle phase), and SD-OCT. ICGA showed BVN with polyps in the macula and blocked fluorescence due to sub retinal hemorrhage in the early and middle phases in the left eye (red dotted circles). There were several bilateral clusters of hyperfluorescent spots in the middle phase of ICGA (yellow arrows). BVN was identified in the right eye during the early and middle stage of ICGA (red dots circles). OCT in the left eye showed RPED, double-layer sign, and retinal cysts (red dotted boxes). OCT in the right eye only showed a corresponding double-layer sign. The inserted images show the direction of OCT scanning.

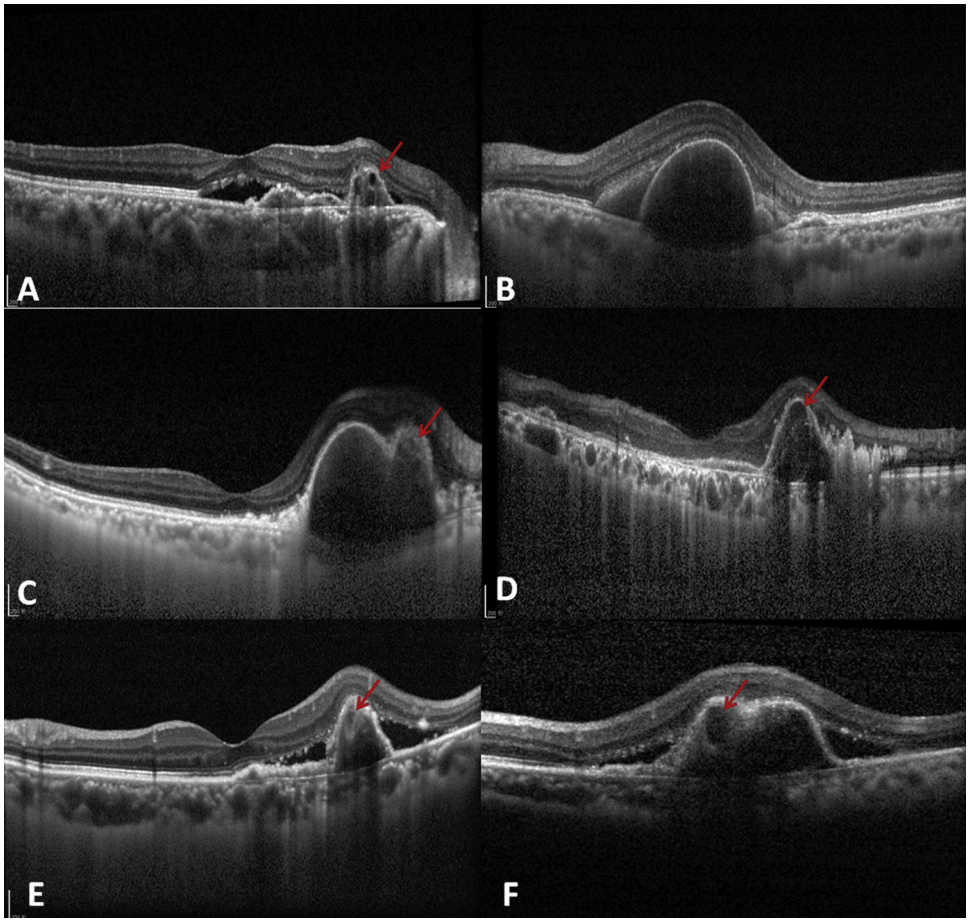

Fig. 2. Illustration of PCV on SD-OCT. Polyps of PCV lesions were directly detected by OCT in A, C, D, E, and F. RPEDs were detected in A–F. Double-layer signs were demonstrated in A, B, D, E, and F.

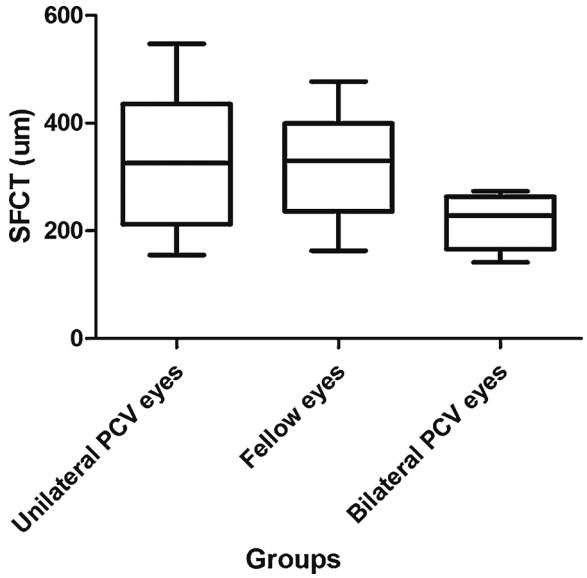

Fig. 3. The measurement of SFCT.

during the early and middle phases. However, OCT of the left eye showed RPED, double-layer sign, and retinal cysts, while only double-layer sign was identified in the right eye according to the BVN in ICGA. Bilateral PCV was diagnosed, although BVN without any leakage was the only symptom found in her right eye (Fig. 1).

4.2. Case 2

A 64-year-old man was diagnosed with PCV in his left eye. ICGA showed bilateral hyperfluorescent spots and late geographic hyperfluorescence during the middle phase. Additionally, BVN with polyps and a hemorrhage RPED were found in his left eye during the early and middle phases. A peripapillary serous retinal detachment was detected in the right eye by ICGA and was confirmed by OCT scanning (Fig. 5).

4.3. Case 3

A 67-year-old man was diagnosed with bilateral PCV. ICGA showed bilateral BVN with polyps and a hemorrhagic RPED in his left eye during the early phase. OCT demonstrated bilateral RPED, double-layer signs, and epi-retinal membrane in his right eye, as well as submacular fluid in his left eye (Fig. 6).

5. Discussion

The pathogenesis of PCV has not been conclusively clarified. The polypoidal vessels are assumed to derive from an abnormality in the inner choroidal vasculature resulting from sclerotic choroidal arteriovenous crossing phenomena [4] and tortuous choroidal vessels with constriction and dilatation [15]. The pathogenic mechanism common to central serous chorioretinopathy might also play a role in the development of PCV lesions through systemic and intraocular pathways.

In our study, 26.4% of patients had bilateral PCV lesions, which was similar to previous reports [2,6], and 18.9% of PCV polyps were directly detected by OCT. However, PCV were noted in 18.2% of fellow eyes, who received bilateral ICGA, according to Hwang`s study [10].

The SFCT in unilateral PCV eyes and their fellow eyes appeared to be similar. Ting, et al., detected no statistically significant difference in SFCT between the study and fellow eyes in PCV patients [16], which was in accordance with our results. Similarly, Wong, et al., reported that patients with unilateral PCV showed choroidal thickening and vascular hyperpermeability in the unaffected fellow eye, considering that the choroidopathy seen in both diseases may be part of a systemic vasculopathy [17]. However, in the present study, bilateral PCV eyes had statistically thinner SFCT than both unilateral PCV eyes and their fellow eyes.

Choroidal vascular hyperpermeability, which is usually related to the BVN evaluated by ICGA and double-layer sign on OCT, might be another risk factor for the development of PCV [12]. Similarly, we found that double-layer sign on OCT had a positive relationship with SFCT in the fellow eyes of the unilateral PCV group. In addition, the percentage of double-layer sign in both unilateral and bilateral PCV eyes was significantly higher than in the fellow eyes of the unilateral PCV group. Moreover, no difference was found in BVN between

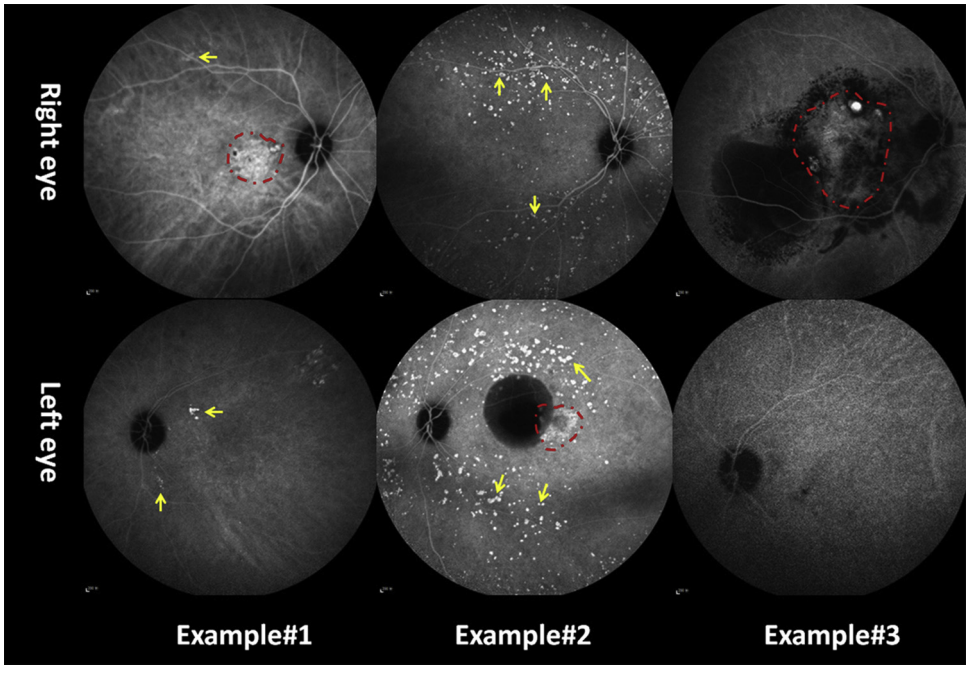

Fig. 4. The demography of PCV (red dotted circles) and bilateral hyperfluorescent spots (yellow arrows) during ICGA.

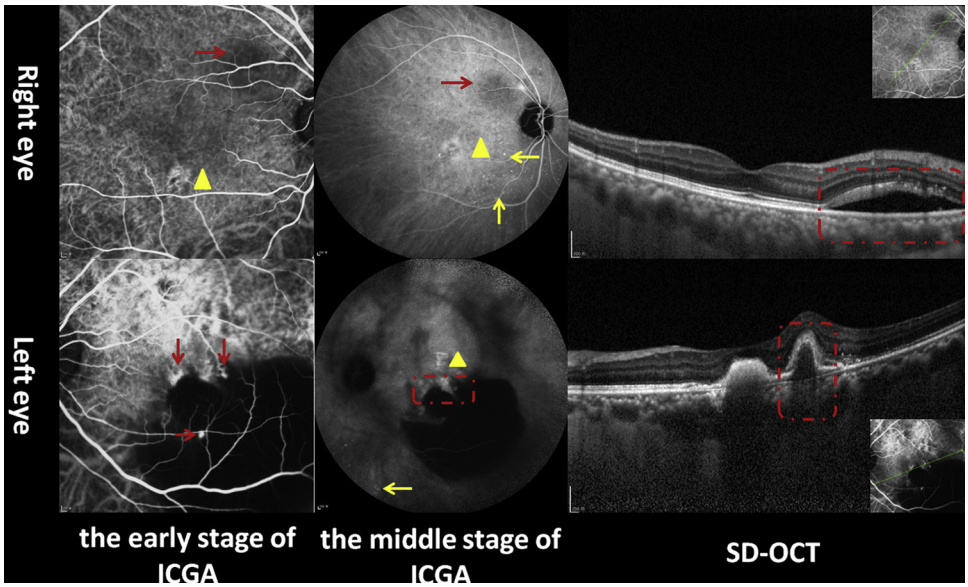

Fig. 5. Illustration of Case 2. ICGA showed BVN with polyps (early stage: red arrows, middle stage: red dots box) and a hemorrhagic RPED in his left eye during the early and middle phases of ICGA, as well as binocular hyperfluorescent spots (yellow arrows) and late geographic hyperfluorescence (yellow triangles) during the middle phase. A peripapillary serous retinal detachment was detected by ICGA (red arrow) and was confirmed by OCT (red dots box) in the right eye. The OCT of the left eye also indicated RPED (red dotted box) due to polypoidal lesions in ICGA. The inserted images show the direction of OCT scanning.

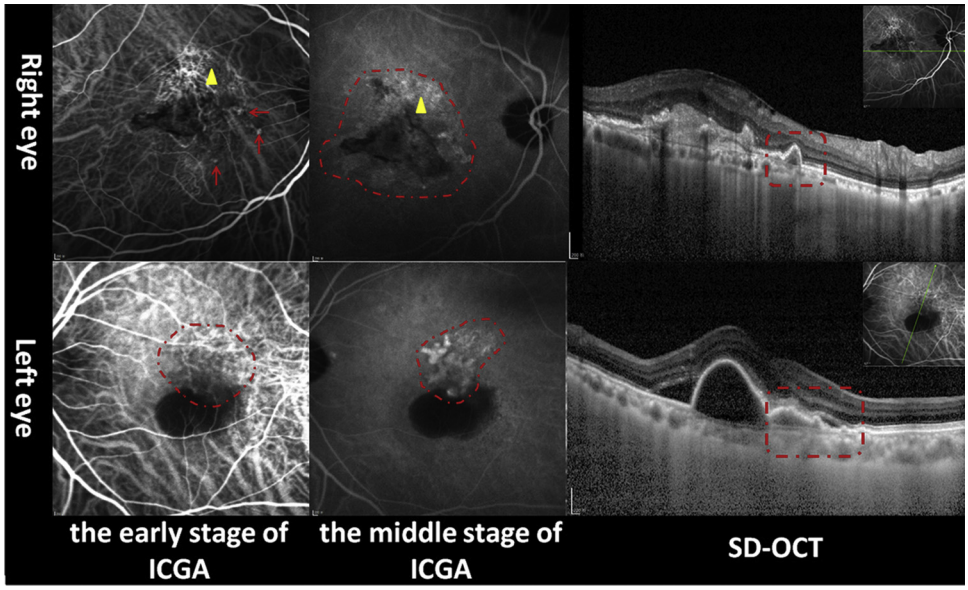

Fig. 6. Illustration of Case 3. ICGA showed BVN with binocular polyps (right: red arrows, left: red dotted circle) and a hemorrhagic RPED in his left eye during the early phase of ICGA and binocular late geographic hyperfluorescence (red dotted circles) during the middle phase of ICGA. OCT demonstrated bilateral RPED, double-layer signs (red dotted boxes), epi-retinal membrane in the right eye, and submacular fluid in the left eye. The inserted images show the direction of OCT scanning.

unilateral (92.3%) and bilateral PCV eyes (71.4%), which was a larger percentage than that in Hwang`s study (45.4%) [10].

However, Koizumi, et al., reported that 80.6% of PCV patients showed bilateral choroidal vascular hyperpermeability [12]. Similarly, Sasahara, et al., also reported that 90% of patients with PCV associated with choroidal vascular hyperpermeability showed bilateral choroidal vascular hyperpermeability [18]. We also found that the proportion of eyes with hyperfluorescent spots in the fellow eyes of the unilateral PCV group was lower than that in both the unilateral and bilateral PCV eyes, while the latter two did not show any significant difference. In a study by Kim, et al., ICGA of the unaffected fellow eyes of 74 patients with unilateral PCV discovered punctate hyperfluorescent spots in 38 eyes, as was previously described in eyes with central serous chorioretinopathy, which may represent leakage from punctate hyperpermeable inner choroid spots or late staining of drusen-like sub-RPE deposits associated with choroidal hyperpermeability [13]. In our study, ICGA-related hyperfluorescent spots were significantly and positively related to SFCT, BVN, RPED, and double-layer sign on OCT. We posit that ICGA-related hyperfluorescent spots may be an important imaging marker for the occurrence and progression of PCV, and that further quantitative analysis should be carried out to specify this parameter.

Choroidal vascular hyperpermeability might arise in eyes with immature BVN, just as choroidal vascular hyperpermeability may be an angiographic feature corresponding to the collagen matrix in the Bruch membrane or extravasated fluid from BVN [14].

Interestingly, two eyes in our study showed macular choroidal BVN without any sign of polyps or activity on ICGA. Abnormal choroidal vascular networks, a proposed origin of PCV lesions, were present before the clinical manifestations of PCV lesions in more than 50% of examined eyes, which also showed high vascular hyperpermeability [19]. We defined this phenomenon as probable or preclinical PCV, which may potentially be a strong angiographic indicator. In clinical settings, ICGA is important for the detection of subclinical PCV lesions and should therefore be bilaterally performed, even in unilaterally affected patients, in order to predict potential clinical deterioration in the fellow eyes of PCV patients [7]. Of the 53 PCV cases, 14 presented with bilateral PCV. Bilateral PCV was not uncommon in another study [20], in which the onset of symptoms in the fellow eyes occurred 10–30 years later, on average, as previously reported [21].

In addition, the drusen tended to prevail in the fellow eyes of the

unilateral PCV group, compared with both unilateral and bilateral PCV eyes. Unlike AMD, the relationship between drusen and PCV is still undefined. Multiple or confluent drusen are considered rare, especially in PCV eyes [7]. In Asian populations, the prevalence of drusen in PCV patients has been shown to be lower than in AMD patients [3,7]. On the contrary, Giovannini, et al., reported that drusen were found in the fellow eyes of 64.1% of unilateral PCV cases significantly [2]. Nevertheless, these results suggest that, at least in Asian populations, pigmentary abnormalities without drusen may be a stronger risk factor for PCV than drusen [19].

These observations argue in favor of a genetic component of PCV [21]. Sakurada, et al., reported that, in age-related maculopathy susceptibility, 2 (ARMS2) A69S variants were associated with the exudative activity of PCV [22] and the ARMS2 A69S variants were also significantly associated with hemorrhagic or subpigment epithelial PCV lesions [23]. The ARMS2 A69S risk allele was significantly more prevalent in patients with second eye involvement compared to those without PCV in the fellow eye. The ARMS2 A69S genotype was identified as a risk factor for developing PCV in the fellow eye. Survival analysis revealed that the fellow eye of patients with the risk-associated homozygous ARMS2 A69S genotype was affected significantly earlier than in patients with other genotypes [24].

Currently, injection with intravitreal anti-vascular endothelial growth factor (VEGF) is major therapeutic strategy for PCV. Long-term improvement in best-corrected visual acuity was noted in 50% of the included PCV patients who received anti-VEGF monotherapy [10]. Moreover, both conbercept and ranibizumab have been reported to effectively increase the visual acuity and to regress polyps in PCV eyes [25]. Similarly, Qu, et al., reported that conbercept therapy led to the complete regression of polyps in more than half of PCV patients [26]. PCV associated with choroidal vascular hyperpermeability was less responsive to anti-VEGF therapy than PCV without choroidal vascular hyperpermeability [10]. Additionally, Ratanasukon, et al., reported that the visual outcomes were comparable between a combination therapy of anti-VEGF injections and rescue or add-on photodynamic therapy vs. monotherapy anti-VEGF injections in PCV treatment [27]. In contrast, Koh, et al., found that combination therapy of ranibizumab plus photodynamic therapy was superior to ranibizumab monotherapy in best-corrected visual acuity and in complete polyp regression, while requiring fewer injections, after 12 months. They recommend that combination therapy should be considered for eyes with PCV [28]. However, no relevant clinical trial in bilateral PCV patients has been reported. Recently, the existence and magnitude of treatment effect on fellow un-injected eyes was evaluated, which may be beneficial for both bilateral and unilateral PCV eyes with fellow at risk eyes. For example, Hanhart, et al., reported that unilateral bevacizumab injections often result in reduction of the macular thickness in the fellow un-injected eye with improved visual acuity [29]. The mean central retinal thickness in the untreated fellow eyes decreased from 251.07 ± 40.29 to 235.45 ± 36.21 μm, according to Michalska-Małecka`s study [30].

This retrospective study also had several limitations. For example, the presence of late geographic hyperfluorescence on ICGA in the fellow eye, representing choroidal vascular hyperpermeability, may constitute the diagnosis of preclinical PCV, since it appears to be a significant risk factor for the development of active PCV [12]. However, late geographic hyperfluorescence was not analyzed in the present study with such a small sample size. Moreover, we did not test the ARMS2 A69S genotype in both unilateral and bilateral PCV cases. This will be considered in further research.

In conclusion, our results indicate that SFCT, ICGA related hyperfluorescent spots, and drusen were the main different imaging characteristics between unilateral and bilateral PCV cases. However, the difference in SFCT, the rate of BVN, and hyperfluorescent spots among bilateral and unilateral PCV eyes and their fellow eyes, suggest that the study of whether or not PCV is a binocular disease still requires further follow up and investigation.

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Competing interests

The authors declare that they have no competing interests.

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