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Original Article

Time-Lag between Subretinal Fluid and Pigment Epithelial Detachment Reduction after Polypoidal Choroidal Vasculopathy Treatment

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Purpose: The goal of the present research was to study post-treatment changes in polypoidal choroidal vasculopathy (PCV) shown by optical coherence tomography (OCT).

Methods: The study included 12 patients with naive PCV. Photodynamic therapy and 3 consecutive intravitreal bevacizumab injections at 6-week intervals were given. Best corrected visual acuity, subretinal fluid (SRF), pigment epithelium detachment (PED), central macular thickness (CMT), and total macular volume (TMV) were measured before and after treatment as assessed by Stratus OCT3.

Results: After treatment, the SRF height decreased earlier than the PED height. The SRF diameter decreased with statistical significance. However, the PED diameter did not show a statistically significant improvement, persisting at pre-treatment levels. Both CMT and TMV decreased significantly after treatment.

Conclusions: After PCV treatment, SRF and PED stabilized, as shown by OCT. However, the PED treatment response was both delayed and refractory compared to the SRF response. The small change in post-treatment PED diameter may suggest the possibility of PCV recurrence.

Key Words: Optical coherence tomography, Pigment epithelial detachment, Polypoidal choroidal vasculopathy

Polypoidal choroidal vasculopathy (PCV) is a clinical disease entity featuring a branching vascular network terminating in polypoidal lesions [1-8]. PCV pathophysiology is not fully understood [9] but many inner choroidal vessel abnormalities have been reported. PCV clinical findings include elevated orange-red lesions on fundus photography and characteristic polypoidal lesions on indocyanine green angiography (ICG). The polypoidal lesions apparently correspond to the lesions on fundus photography.

ICG is an essential test for the diagnosis of PCV; on ICG, branching network vessels and terminating polyps can be identified [10,11]. However, ICG is an invasive technique involving an intravenous indocyanine green dye injection. Optical coherence tomography (OCT) is both non-invasive and supportive when used to diagnose PCV and can monitor changes in various retinal disease states. An OCT image of a PCV eye shows a moderate-to-high reflective polypoidal lesion, 2 reflective retinal pigment epithelium layer lines (termed the double-layer line), subretinal fluid (SRF), and pigment epithelium detachment (PED). Polypoidal lesions and dilated network vessels have been detected in various retinal areas of PCV patients, and can be distributed in the subfoveal [12,13], juxtafoveal, or extrafoveal regions [14]. PCV treatment methods include laser photocoagulation [15-17], photodynamic therapy (PDT) [18-24], and use of anti-vascular endothelial growth factor (anti-VEGF) drugs such as bevacizumab or ranibizumab. In a study regarding the long-term results of PDT treatment for PCV, Akaza et al. [18] found a high incidence of polypoidal lesion recurrence and a frequent need for additional treatment. To address these problems, many authors have explored anti-VEGF treatments for PCV patients.

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Many previous studies have assessed follow-up PCV pathologic changes by ICG or fluorescein angiography (FA) [11]. However, to the best of our knowledge, no report has focused on OCT changes during follow-up after treatment. The authors of the present study hypothesized OCT could be used to explore features of subfoveal or juxtafoveal PCV located near the macula. The present study describes the follow-up changes observed by OCT after PDT/bevacizumab treatment for PCV.

Materials and Methods

The present study included 12 eyes of 12 PCV patients who underwent PDT and 3 consecutive intravitreal bevacizumab injections at 6-week-intervals, at the the Asan Medical Center, Seoul, Korea, from March 2007 to December 2007. All examinations and investigations adhered to the tenets of the Declaration of Helsinki. This study was approved by the Asan Medical Center Institutional Review Board.

Inclusion criteria were 1) symptom onset under 3 months; 2) confirmed polyps and branching vascular networks as seen by ICG; 3) visible SRF or PED on OCT images; 4) visual acuity above 20 / 200; 5) subfoveal (within the foveal avascular zone [FAZ]) or juxtafoveal (within 1-119 μm from the FAZ) PCV lesion areas that could be followed-up using OCT; and 6) a follow-up period longer than 12 months. Exclusion criteria were 1) extrafoveal pathologic PCV that could not be examined by routine OCT scanning; 2) choroidal neovascularization of any other origin such as high myopia, uveitis, or trauma; 3) a previous operation history (in the past 6 months); or, 4) a history of adverse side-effects to verteporfin or ICG dyes.

The best corrective visual acuity (BCVA) was measured and slit lamp examinations, fundus photography, ICG, and OCT were performed at baseline. After confirmation of PCV diagnosis, 3 consecutive intravitreal bevacizumab injections (1.25 mg/0.05 mL), at 6-week intervals, were given. One week after the first bevacizumab injection, PDT employing verteporfin, covering all possible polyps and branching network vessels, was performed. The patients visited for follow-up 1, 3, 6, 9, and 12 months after the first treatment. Each patient received BCVA measurement, slit lamp examination, and OCT on each visit. If there was evidence of recurrence, ICG was repeated at the discretion of the attending clinician. If recurrence was evidenced by new polyps on ICG, decreased visual acuity (VA), or increasing SRF or PED, additional treatment (PDT or an intravitreal bevacizumab injection) was administered.

OCT images were acquired using Stratus OCT3 ver. 4.0.1 (Carl Zeiss Meditec Inc, Dublin, CA, USA). Central macular thickness (CMT), total macular volume (TMV), and PED/SRF heights and diameters were measured. CMT and TMV values were calculated by the Stratus OCT program software. Standard OCT scans were obtained using foveae as fixation points. To permit comparison of changes in OCT findings, scanning directions were kept constant at all follow-up visits, using a standard macular mapping protocol. Two investigators (JBC and JYL) independently measured SRF and PED heights and diameters using a Photoshop length-measuring program (Adobe Systems, San Jose, CA, USA) (Fig. 1).

BCVA measurements, heights and diameters of SRF/PED, and CMT and TMV data were compared between baseline, and 1, 3, 6, 9, and 12 months post treatment. Furthermore, the effects of additional treatments were analyzed. Statistical comparisons were made using the Wilcoxon signed rank test submodule of SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Characteristics of the 12 polypoidal choroidal vasculopathy patients

Characteristics		Data
Male/Female		8 (67)/4 (33)
Age (yr)		69 ± 6.45
Location of polyp	Subfoveal	4 (33)
	Juxtafoveal	8 (67)
Number of PDT sessions		1.25 ± 0.452
Number of intravitreal bevacizumab injections		4.08 ± 1.83
Baseline BCVA (logMAR)		0.3 ± 0.23
Twelve-month BCVA (logMAR)		0.38 ± 0.14

Data are presented as number (%).
PDT = photodynamic therapy; BCVA = best corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

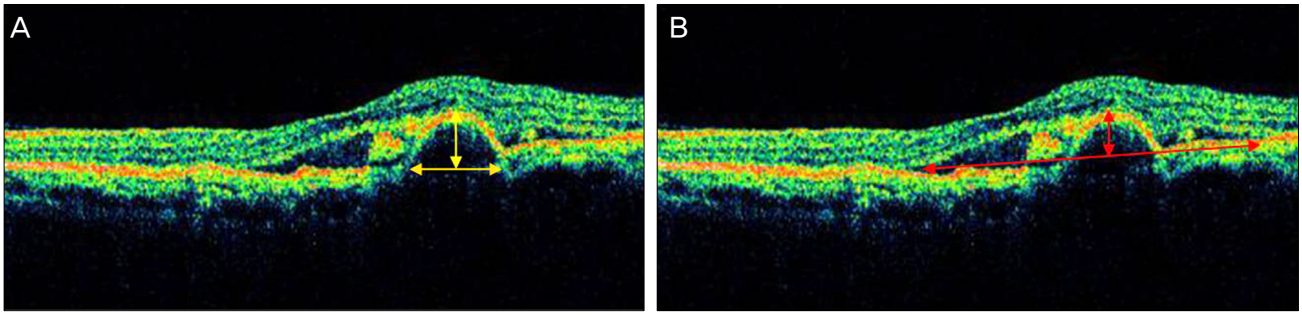

Fig. 1. Heights and diameters of pigment epithelium detachment (PED) and subretinal fluid (SRF). The same scan direction was used at all follow-up visits to yield PED data (A) and SRF information (B).

Results

Baseline characteristics and clinical data of the 12 patients are summarized in Table 1. The mean patient age was 69 years. In 4 patients, polyps were located in the subfoveal area, and in the other 8 patients, polyps were located in the juxtafoveal area. In addition to the first 3 consecutive bevacizumab injections and the single PDT treatment, 2 patients received repeated PDT treatments whereas 5 patients were prescribed a single extra bevacizumab injection (Table 1). Figs. 2 and 3 provide information on 2 of the 12 patients. SRF and PED height change responses, as observed on OCT, showed different patterns (Fig. 4). Compared to baseline, SRF height decreased significantly at the 1-, 3-, 6-, 9-, and 12-month follow-ups (*p*-values 0.008, 0.008, 0.012, 0.043, and 0.018, respectively). PED height also decreased with time, however treatment response was delayed. At the 1- and 3-month follow-ups, PED heights showed no statistically significant decreases (*p*-values 0.138 and 0.109, respectively). However, at the 6- and 9-month follow-ups, clinically significant decreases in PED heights were observed (*p*-values 0.018 and 0.028, respectively). At the 12-month follow-up, PED height had increased and a tendency toward disease recurrence was observed.

SRF and PED diameter changes, measured by OCT, are shown in Fig. 5. The SRF diameter decreased significantly at

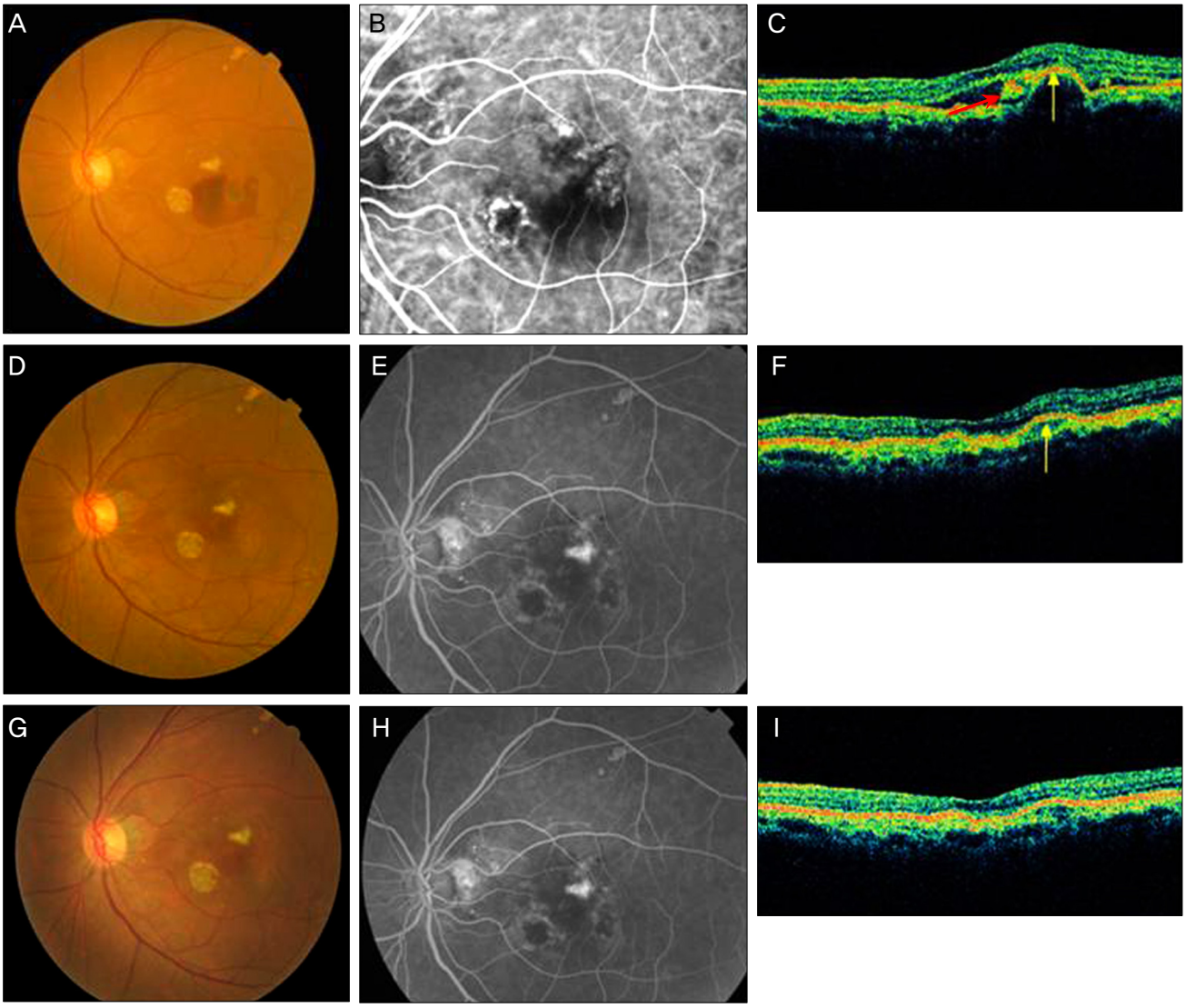

Fig. 2. Polypoidal choroidal vasculopathy in the left eye of a woman 61 years of age. Fundus photography showed retinal hemorrhage (A). Indocyanine green angiography (ICG) revealed polyps and network vessels (B). An optical coherence tomography (OCT) transverse scan showed the polypoidal lesion (red arrow) and dome-shaped pigment epithelium detachment (PED) (yellow arrow) (C). After 6 months, the hemorrhage disappeared (D), and no active leakage was seen on fluorescein angiography (E). Follow-up ICG was not performed. OCT showed a decrease in PED height but a PED diameter persistently greater than normal (yellow arrow); subretinal fluid was absent (F). Twelve months later, there was no hemorrhagic lesion on fundus examination (G,H), however OCT showed persistence of the abnormally large PED diameter (I).

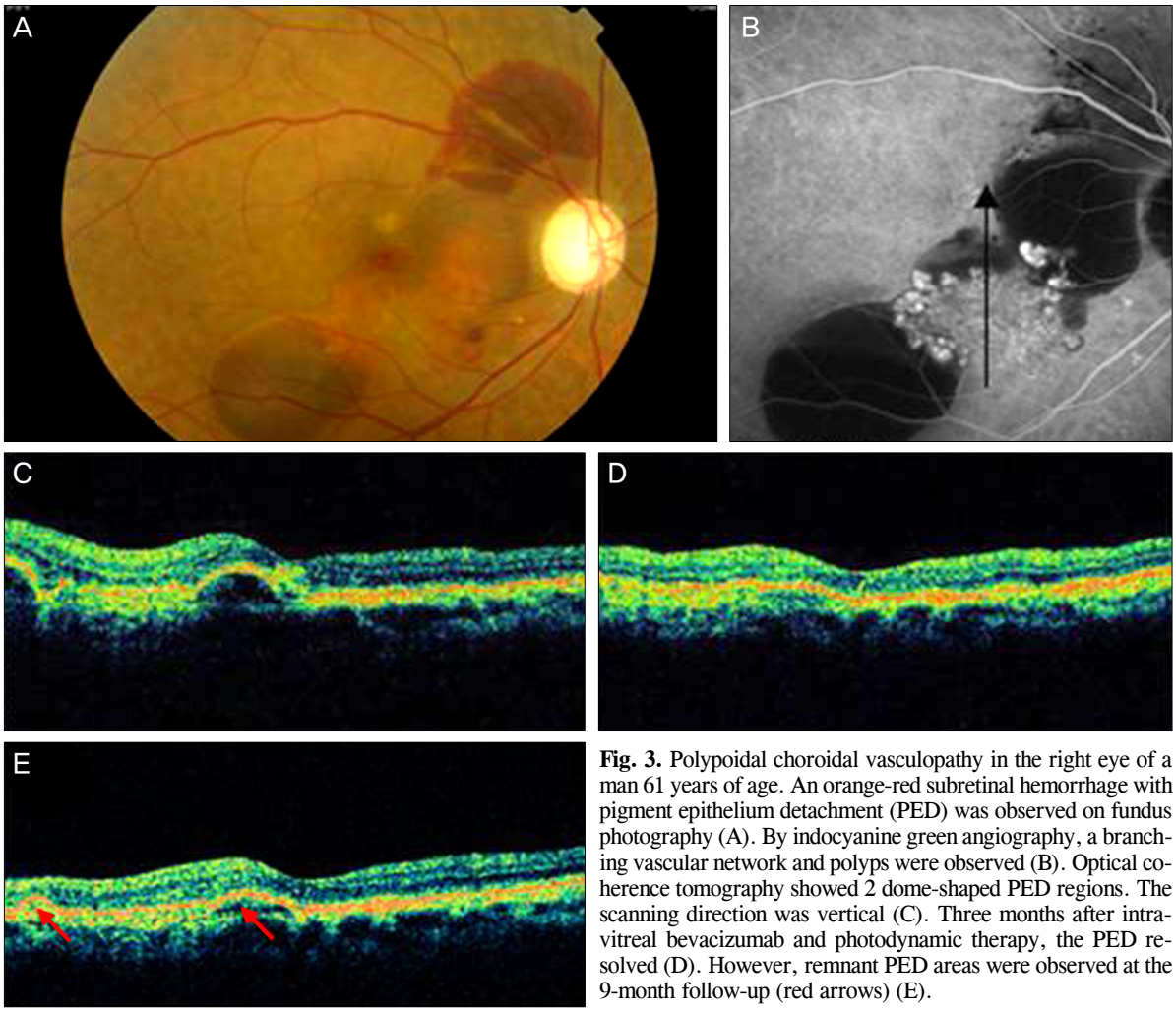

Fig. 3. Polypoidal choroidal vasculopathy in the right eye of a man 61 years of age. An orange-red subretinal hemorrhage with pigment epithelium detachment (PED) was observed on fundus photography (A). By indocyanine green angiography, a branching vascular network and polyps were observed (B). Optical coherence tomography showed 2 dome-shaped PED regions. The scanning direction was vertical (C). Three months after intravitreal bevacizumab and photodynamic therapy, the PED resolved (D). However, remnant PED areas were observed at the 9-month follow-up (red arrows) (E).

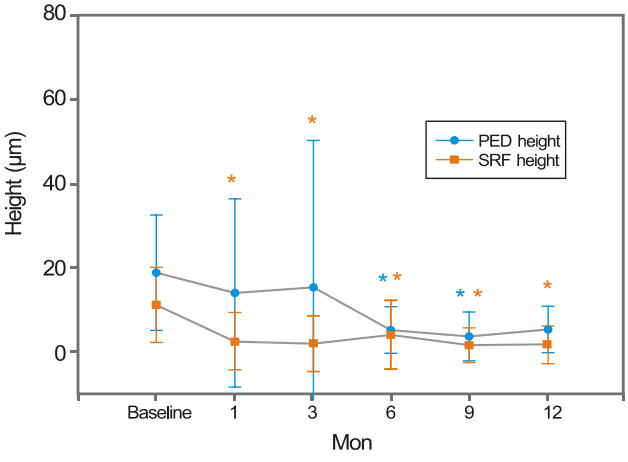

Fig. 4. Mean (± standard deviation) pigment epithelium detachment (PED) and subretinal fluid (SRF) heights of 12 polypoidal choroidal vasculopathy patients at baseline and all follow-ups. SRF height decreased at 1-,3-,6-,9- and 12-month follow-ups with clinical significance. PED heights showed no statistically significant decreases at the 1- and 3-month follow-ups. However, at the 6- and 9-month follow-ups, clinically significant decreases in the PED heights were observed.

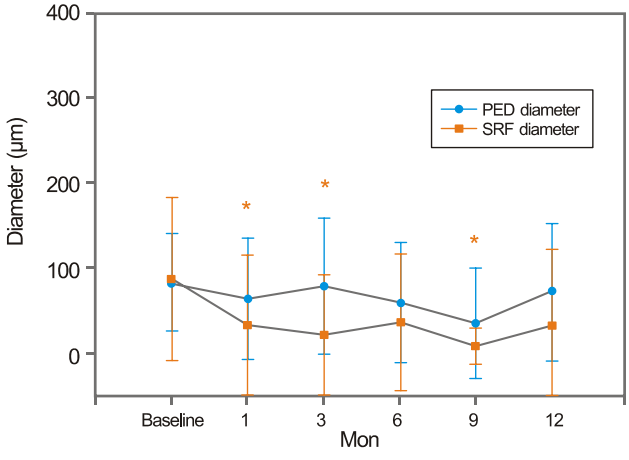

Fig. 5. Pigment epithelium detachment (PED) and subretinal fluid (SRF) diameters at baseline and all follow-ups. The SRF diameter decreased with clinical and statistical significance at the 1-, 3-, and 9-month follow-ups (*p*-values 0.005, 0.013, and 0.043 respectively). However, there was no significant decrease in PED diameter at any follow-up.

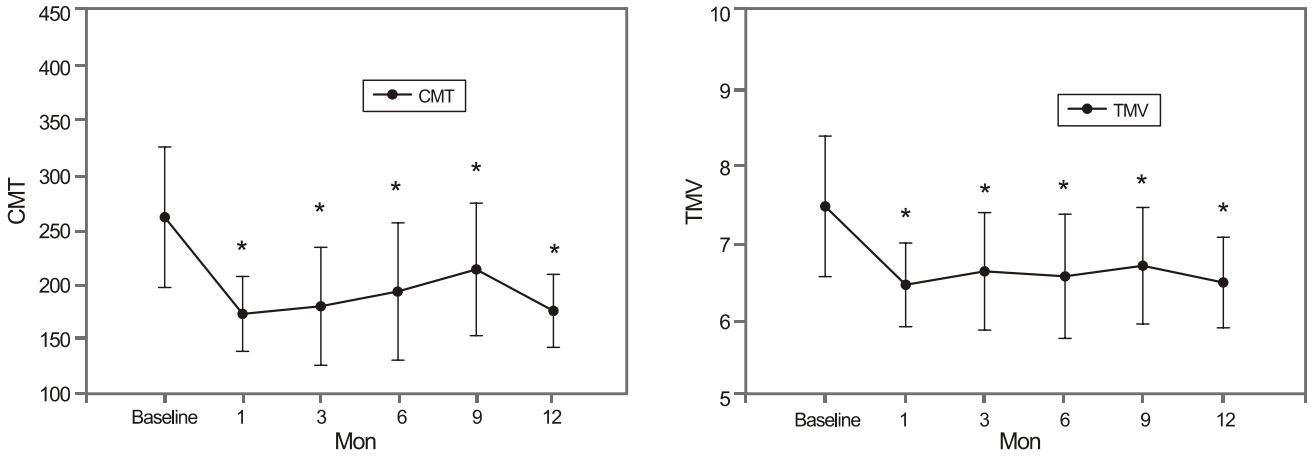

Fig. 6. Central macular thickness (CMT) and total macular volume (TMV) of polypoidal choroidal vasculopathy patients at all follow-ups. Both CMT and TMV showed statistically significant decreases at all follow-up examinations.

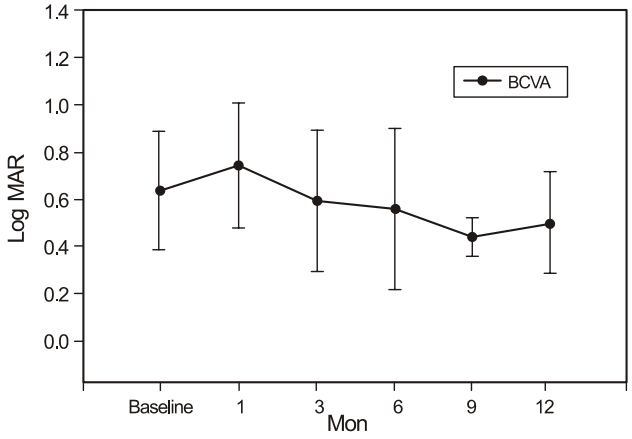

Fig. 7. Best corrected visual acuity (BCVA) measurements at baseline and at all follow-ups. BCVA showed a tendency toward improvement, however this was neither clinically nor statistically significant. logMAR = logarithm of the minimum angle of resolution.

the 1-, 3-, and 9-month follow-ups (*p*-values 0.005, 0.013, and 0.043, respectively). Notably, the PED diameter (as estimated by OCT) did not show a statistically significant decrease at any follow-up. The PED diameter did not respond to even multiple PCV treatments, unlike what was noted when PED height was assessed.

TMV and CMT measurements by OCT are shown in Fig. 6. At all follow-up visits, clinically significant improvements were observed. Although the VA tended to improve, the VA data did not attain statistical significance (Fig. 7).

Discussion

PCV features a polypoidal lesion with a branching vascular network accompanied by serous or hemorrhagic PED. Polyps and branching vascular networks detectable by ICG are specific findings that distinguish PCV from age-related macular degeneration (AMD). Many investigators have explored PCV pathology using various OCT instruments. In previous studies, PCV polypoidal lesions appeared as moderate-to-highly reflective lesions on OCT. The branching vascular network vessels show as 2 distinct reflective lines; the phenomenon has been termed the 'double-layer sign'. The reflective line components have not yet been identified by histopathology or microscopy [25]. Compared to AMD, the PED of PCV is more elevated, the lesion is dome-shaped, and fewer intraretinal cystic lesions are seen. PED is more prominent in PCV than in AMD. Although many OCT features of PCV have been described, reports on follow-up changes observed by OCT are few in number. Therefore, the authors herein report PCV changes after treatment with PDT/intravitreal bevacizumab. In the present study, changes in PED/SRF heights and diameters were assessed. Treatment responses differed when PED and SRF were compared and SRF reduction preceded a fall in PED. However, the PED diameter did not respond to PDT/intravitreal bevacizumab treatment. Both SRF diameter and height showed clinically significant decreases, but the PED diameter decreased only slightly, without clinical significance. In a recent study of PED pathophysiology, Tsujikawa and associates showed the branching vascular network and polyps were near or in the PED [26]. Lee et al. [27] reported PDT could not eliminate network vessels; new vessels were seen on ICG after PDT. The continuing enlarged PED diameter, except for a slight reduction at the 9-month follow-up observed in the present study, implies the possibility of branching vascular network persistence despite treatment. However, the present data also show OCT is valuable in monitoring patients for such recurrence after treatment.

In the present study, 7 out of 12 patients (58%) required additional treatment, either PDT (2 cases) or a single intraocular bevacizumab injection (5 cases) after the initial combination treatment. Many investigators have reported PCV is both recurrent and refractory to treatment. Akaza et al. [18] reported a high PCV polypoidal lesion recurrence incidence

after PDT treatment in a study featuring 2 years of follow-up. Yamashiro et al. [28] found a 40% PCV recurrence rate after PDT [28]. Thus, careful follow-up examinations are essential for PCV patients. OCT can conveniently monitor changes and identify when re-treatment is indicated. Although both ICG and FA can show PCV pathologic features more precisely than OCT, the former methods are both more invasive and inconvenient (for both patients and attending physicians) than OCT.

Although the VA tended to improve after treatment at any point, the statistical significance was not attained. VA decreased slightly between the 9-month and 12-month follow-ups. This may signify incipient PCV recurrence.

The present study had a size limitation (12 cases). However, the inclusion criteria were restricted to exclude selection bias. Only naïve patients with subfoveal or juxtafoveal PCV were recruited and examined. In such patients, OCT can monitor PCV lesions because the OCT scan length is 6 mm. Lesions were examined at all follow-up visits. However, future studies with larger patient numbers are required. To the best of our knowledge, no report on OCT post-treatment follow-up of PED or SRF has appeared. PED and SRF greatly affect VA and reflect PCV disease status. OCT permits PED and SRF changes to be compared. Furthermore, OCT can identify a need for re-treatment.

In conclusion, despite treatment with PDT/intravitreal bevacizumab, PED regressed only incompletely and remnant PED bases were seen by OCT. PDT/bevacizumab treatment achieved SRF reduction and VA improvement. However, the persistence of the PED diameter enlargement observed on OCT despite treatment may suggest the possibility of PCV recurrence. The results from the present study indicate that PCV patients need careful follow-up.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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