

The use of optical coherence tomography angiography in pachychoroid spectrum diseases: a concurrent comparison with dye angiography

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Abstract

Purpose The study objective was to compare dye angiography and optical coherence tomography angiography (OCTA) in detecting choroidal neovascularization (CNV) in patients presenting with pachychoroid features and flat irregular pigment epithelial detachment (PED).

Methods Nineteen eyes of 17 patients, presenting with flat PED and pachychoroid features, and without age-related macular degeneration or any other degenerative change, were analyzed. Fluorescein angiography (FA)/Indocyanine green angiography (ICGA) and OCTA were performed during the same visit. Subfoveal choroidal thickness was measured by enhanced depth imaging using spectral domain optical coherence tomography.

Results The mean age of the patients was 59.1 years. Mean subfoveal choroidal thickness was 388 μm . FA revealed non-patognomic features including RPE alterations, window defects, leaking points and leakage from an undetermined source. ICGA revealed choroidal vascular plaque in eight eyes (42%) and suspicious plaque in five eyes (26%). Nonneovascular features, such as hyperpermeability or dilated choroidal vessels, were observed in six eyes (32%). OCTA showed choroidal neovascularization in 14 (74%). For all of the eyes, which ICGA was positive for presence of CNV, OCTA also showed CNV, and in one case it also revealed polypoidal characteristics of the neovascular network. OCTA

was also able to detect CNV in all of the eyes with suspicious plaque, and in one eye without CNV appearance using ICGA. **Conclusions** OCTA demonstrated greater sensitivity in detecting type 1 CNV than conventional dye angiography in cases with pachychoroid spectrum disease.

Keywords Flat irregular retinal pigment epithelium detachment · Optical coherence tomography angiography · Indocyanine green angiography · Pachychoroid neovasculopathy

Introduction

Pachychoroid-related macular disorders are a spectrum of diseases that share common features, such as increased choroidal thickness and dilated outer choroidal vessels [1]. This spectrum includes four different clinical entities; pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSCR), pachychoroid neovasculopathy (PNV), and polypoidal choroidal vasculopathy (PCV) [2].

PPE is the new term used to define a permanent and abnormal increase in choroidal thickness, often manifesting as dilatation of the large outer oval choroidal vessels (Haller's layer), and which compress the overlying choriocapillaris and Sattler's layer without causing subretinal fluid (SRF) [2–4]. Pachychoroid neovasculopathy is a recently proposed clinical entity in choroidal neovascularization (CNV) [5]. It has the features of type 1 neovascularization and choroidal thickening in the absence of characteristic age-related macular degeneration (AMD) or degenerative change.

Pachychoroid spectrum diseases may show pigment epithelium detachments (PED) in variable shape and size. Pigment epithelium detachments were seen in more than two thirds of the CSCR [6]. While acute CSCR usually

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reveals typical dome-shaped PEDs, flat irregular PED was generally observed in chronic CSCR and are defined as the irregular elevation of the retinal pigment epithelium (RPE), allowing visualization of the underlying Bruch's membrane.

Complete or partial hyperreflectivity might be observed in the sub-RPE area in flat PED. Hyper-reflectivity of the material may be caused by neovascular tissue or optic material accumulation. It was reported that one third of flat, irregular PED in CSCR contained CNV [7]. If underlying type 1 CNV is present, the early detection of underlying neovascular tissue and the ability to make a distinction between these and AMD cases is essential to ensure accurate treatment planning.

Recently, the high sensitivity and specificity of optical coherence angiography (OCTA) in identifying CNV in eyes with chronic CSCR and pachychoroid spectrum disease was demonstrated in the literature [8–13]. Thus, the study objective was to detect the presence of a neovascular membrane underlying flat, irregular PED in patients presenting with pachychoroid features through the concurrent use of OCTA, fluorescein angiography (FA) and indocyanine green angiography (ICGA). The concurrent use of imaging techniques expedited an evaluation of the pathologic features without the time delay inherent in different follow-up visits and differences in the morphologic appearance. We hypothesized that the results of this comparison would help clinicians to more precisely detect which of the two imaging techniques had greater diagnostic sensitivity.

Method

The eyes of patients presenting with flat PED and pachychoroid features, and without age-related macular degeneration (AMD) or any other degenerative change, were analyzed in this observational consecutive case series. Nineteen eyes of 17 patients presenting with flat irregular PED at the Department of Ophthalmology, Ankara University, Ankara, Turkey, were included in the study. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the participants prior to enrolment.

Inclusion criteria for participation in the study were the presence of flat, irregular PED, accompanied by dilated choroidal vessels, or increased choroid thickness, and/or a history of CSCR. Patients with a history of inflammatory ocular disease or macular drusen were excluded.

The participants underwent a thorough ophthalmic assessment that included best corrected visual acuity (BCVA), slit lamp biomicroscopy, and a dilated funduscopy examination. Spectral-domain optical coherence tomography (SD-OCT) (Spectralis[®], Heidelberg Engineering Inc., Heidelberg, Germany), FA and ICGA (Heidelberg Retina Angiograph 2[®]; Heidelberg Engineering, Heidelberg, Germany), OCTA

(Avanti RT Vue XR[®] with AngioVue[®] software; Optovue Inc., Fremont, CA, USA) were performed for all patients.

Subfoveal choroidal thickness (SFCT) measurement, defined as the distance from the outer portion of the hyper-reflective line (corresponding to the RPE) to the inner surface of the choroidal-scleral junction, was performed using enhanced depth imaging (EDI)-OCT scans. The diameter of the thickest choroid vessel under the flat PED was measured using a manual caliper to determine the widest distance between the two vessel walls. Fundus fluorescein angiography, ICGA and OCTA were concurrently performed on all the patients. According to the ICGA findings, the lesions were classified as choroidal vascular plaque, suspicious plaque, and ones with nonneovascular characteristics, such as choroidal hyperpermeability or dilated choroidal vessels. Finally, imaging was performed using SD-OCT (OCTA software) on a commercially available device operating at 70,000 A-scans per second to acquire OCTA volumes for all patients concurrently with dye angiography. The OCTA scans were examined for the presence or absence of type 1 neovascular tissue. One retina specialist (SD) who was experienced in the interpretation of the OCTA, FA and ICGA read the images regarding the CNV presence in a blind fashion. The interpretation of the OCTA and FA-ICGA images were performed at different times in order not to be affected by image memory.

Statistical analysis was performed using SPSS[®] software for Windows[®] version 15.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as mean \pm standard deviation for the continuous variables. A *p*-value of <0.05 was considered to be statistically significant.

Results

Nineteen eyes of seventeen patients were included in the study. Eleven of the patients (65%) were men and six (35%) were women. The mean age of the patients was 59.1 years (± 7.7). Before multimodal imaging tests, a preliminary diagnosis of CSCR had been given for 15 eyes (79%) and one of AMD for four eyes (21%). Concurrent EDI-OCT, FA, ICGA, and OCTA images were taken from the patients. The EDI-OCT images revealed flat, irregular PED and pachychoroid features, i.e., increased subfoveal choroidal thickness and the presence of pachyvessels. None of the patients were shown to have drusen or hemorrhage on clinical examination or imaging. Sixteen eyes contained SRF at the baseline examination (Table 1). FA revealed non-pathognomic features including RPE alterations, window defects, leaking points and leakage from an undetermined source. Choroidal vascular plaque was shown on ICGA in eight eyes (42%) and suspicious plaque in five eyes (26%), as well as nonneovascular features, such as hyperpermeability and dilated choroidal vessels, in six eyes (32%). Choroidal neovascularization was shown using OCTA

Table 1 The multimodal imaging features of the cases

PATIENT	SIDE	AGE	EDI-OCT	FFA	ICGA	OCTA
Patient 1	OS	45	SRF Flat irregular PED Serous PED	RPE alterations, Window defect, Enlarging leaking point	Suspicious plaque	Type 1 CNV
Patient 2	OS	52	SRF Flat irregular PED	Window defect, Multiple enlarging leaking points in the late phase	Hyperpermeability	No lesion
Patient 3	OS	61	SRF Flat irregular PED	Diffuse RPE alterations, Window defect	Suspicious plaque	Type 1 CNV
Patient 4	OD	71	SRF Flat irregular PED	Diffuse RPE alterations, Window defect	Plaque	Polyp + CNV
Patient 5	OS	55	SRF Flat irregular PED	RPE alterations, Staining scar tissue, Leakage from undetermined source	Plaque	Type 1 CNV
Patient 6	OS	75	SRF Flat irregular PED	Late leakage from undetermined source	Dilated choroidal vessels	Type 1 CNV
Patient 7	OD	54	SRF Flat irregular PED	Multiple enlarging leaking points from RPE	Suspicious plaque	Type 1 CNV
Patient 8	OD	70	SRF Flat irregular PED	RPE alterations, Minimal leaking points from RPE	Suspicious plaque	Type 1 CNV
Patient 9	OS	63	SRF Flat irregular PED	Diffuse RPE alterations, Window defect	Plaque	Type 1 CNV
Patient 10	OD	54	SRF Flat irregular PED	Diffuse RPE alterations, Window defect	Plaque	Type 1 CNV
Patient 11	OD	63	Flat irregular PED	Window defect at the fovea, Gravitational defect throughout inferior venous arcade	Plaque	Type 1 CNV
Patient 11	OS	63	Flat irregular PED	Window defect at the fovea, Multiple leaking points in parafoveal region	Plaque	Type 1 CNV
Patient 12	OS	54	SRF Flat irregular PED	Diffuse RPE alterations, Minor leaking points	Suspicious plaque	Type 1 CNV
Patient 13	OD	62	SRF Flat irregular PED	Leakage from undetermined source	Plaque	Type 1 CNV
Patient 13	OS	62	Flat irregular PED	Leakage from undetermined source	Plaque	Type 1 CNV
Patient 14	OD	51	SRF Flat irregular PED	Multiple leaking points	Hyperpermeability	No lesion
Patient 15	OD	59	SRF Flat irregular PED	Enlarging leaking points	Hyperpermeability	No lesion
Patient 16	OS	57	SRF Flat irregular PED	Multiple enlarging leaking points from RPE	Hyperpermeability	No lesion
Patient 17	OD	52	SRF Flat irregular PED	RPE alterations, Window defect	Hyperpermeability	No lesion

in 14 eyes (74%). For all of the eyes for which ICGA was positive for presence of CNV, OCTA also showed CNV, and in one case (case 4) it also revealed polypoidal characteristics of the neovascular network (Fig 1). OCTA was also able to detect CNV in all of the eyes with suspicious plaque, and in one eye without CNV appearance using ICGA (Fig 2). Five cases were found to be CNV negative using ICGA and OCTA (Fig 3). Overall, OCTA was able to identify CNV in six eyes in which apparent plaque appearance was not found with ICGA.

Mean best-corrected visual acuity was 0.5 (0.05–1.0) snellen line at the baseline visit. Mean SFCT was 388 μm (a range of 186–558 μm) and mean choroidal vessel thickness was 224 μm (a range of 107–365 μm). The patients were treated with intravitreal injections of ranibizumab (Lucentis[®]; Novartis Pharma AG, Basel Switzerland) and/or aflibercept (Eylea[®]; Bayer Schweiz AG, Zurich, Switzerland), photodynamic therapy (PDT), subthreshold micropulse laser (yellow wavelength of 577 nm) (Supra Scan 577[®]; Quantel Medical, Clermont-Ferrand, France), or with a combination of these modalities. The mean follow-up time was 30.5 months (a range of 1–119 months). The mean BCVA at the last visit was 0.5 (0.1–1.0) snellen line. The mean SFCT was 330 μm (a range of 148–525 μm) and the mean choroidal vessel thickness was 171 μm (a range of 67–310 μm). The treatment modalities and

outcomes of the patients are summarized in Table 2. Five (29%) of the cases responded well to single or two sessions of laser therapy or intravitreal aflibercept injections and remained fluid free for a prolonged time. Significant SFCT reduction was more effectively evident with PDT. However, seven (41%) of the cases were more resistant to monotherapy, and were controlled only by a long lasting combination therapy. Intravitreal ranibizumab injection was not as effective in these cases.

Discussion

Multimodal imaging data were compared with the data obtained through the concurrent use of OCTA in the current study on a series of 19 eyes with shallow, irregular PED within the pachychoroid clinical spectrum. We found the OCTA findings to be far superior and sensitive in detecting type 1 choroidal new vessels in these patients, compared to conventional dye angiography.

Irregular retinal PED in chronic CSCR was reported to give rise to an increased risk of CNV, when compared to regular retinal PED [14]. Recently, Bousquet et al. [7] evaluated 88 eyes of 61 chronic CSCR patients and reported the presence of

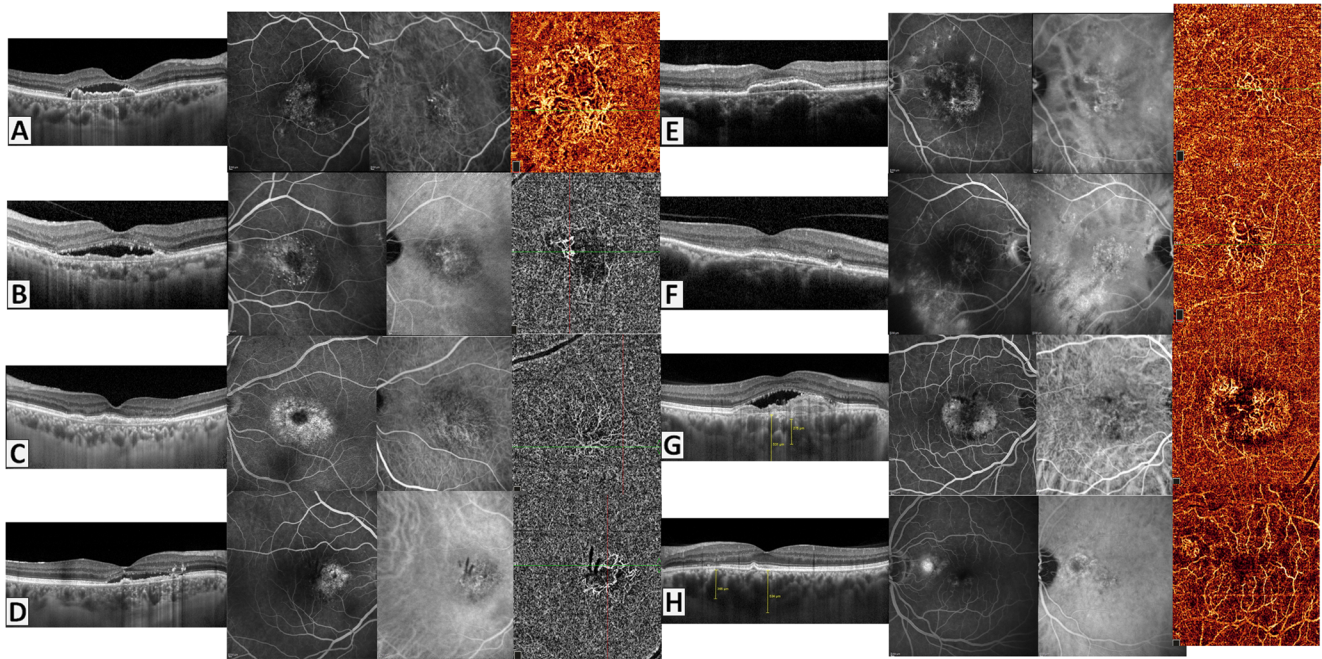


Fig. 1 Imaging findings for cases 4, 5, 9, 10, 11 OD, 11 OS, 13 OD, and 13 OS. A, B, C, D, E, F, G, and H show multimodal imaging of cases 4, 5, 9, 10, 11OD, 11 OS, 13 OD, and 13 OS, respectively, which were characterized by choroidal neovascular plaque on indocyanine green angiography. All of the eyes had irregular, flat epithelial detachment

and pachychoroid features. Subsequent optical coherence tomography angiography revealed prominent neovascular membrane in all the cases. In addition, it demonstrated polypoidal enlargement in case 4 (A). Both the eyes of patient 11 remained fluid free during the 34-month follow-up, and this was recognized to be silent choroidal neovascularization

flat irregular PED in 59 eyes of 51 patients. Previously, Hage et al. [15] evaluated the presence of flat, irregular PED in 172 eyes of 110 chronic CSC patients and reported that 53 of the eyes of 38 patients had flat irregular PED. Also, they showed the presence of type 1 CNV in 19% of the eyes with flat, irregular, retinal PED by multimodal imaging of the fundus. The authors indicated that although they used several

multimodal imaging facilities, distinguishing between avascular, flat PED and the early stages of type 1 CNV was challenging. Conventional dye angiographies may be limited in visualizing CNV in CSC. Fluorescein angiography usually reveals stippled early hyperfluorescence and ill-defined late staining, which may be seen in both CNV and wide spread RPE alterations of the CSC. ICGA often reveals midphase patchy

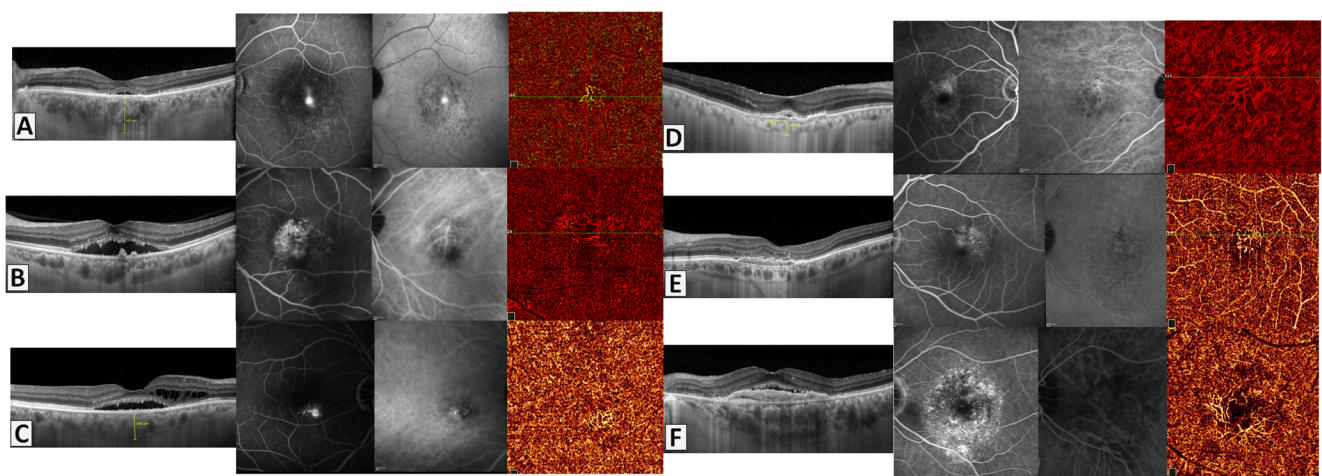


Fig. 2 Imaging findings for cases 1, 3, 6, 7, 8, and 12. Enhanced depth coherence tomography of five cases revealed pachychoroid, pachyvessels, and the absence of drusen. Fluorescein angiography revealed non-patognomic features including RPE alterations, window defect, and leaking points. Indocyanine green angiography showed

suspicious plaque in cases 1, 3, 7, 8, and 12 (A, B, C, D, and E, respectively). It also showed dilated choroidal vessels in case number 6 (F). By contrast, optical coherence angiography successfully indicated type 1 choroidal neovascularization in all cases

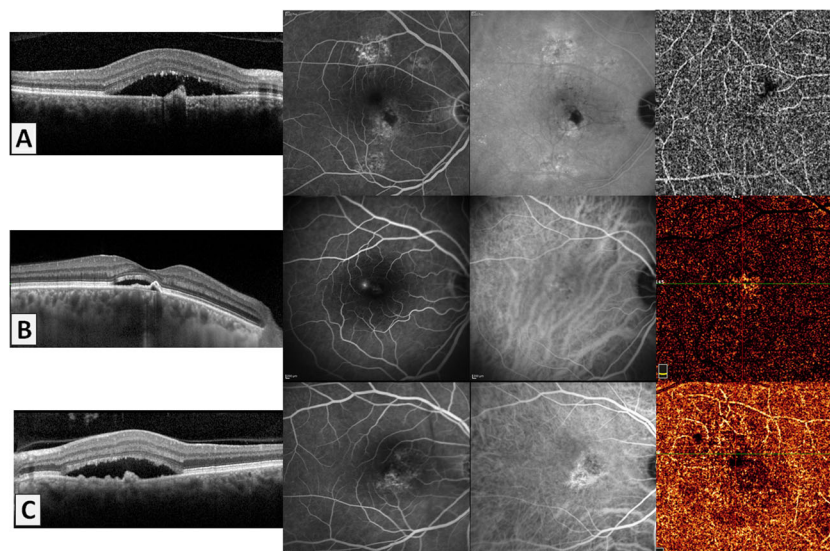


Fig. 3 A comparison of imaging findings in patients 14, 15, and 17. Spectral domain optical coherence tomography of cases 14 (A), 15 (B), and 17 (C) showed pachychoroid, subretinal fluid, and flat, irregular pigment epithelial detachment. Fluorescein angiography revealed leaking points in patients 14,15 and RPE alterations and window defect

in patient 17. Indocyanine green angiography revealed hyperpermeability or dilated choroidal vessels in these cases. Optical coherence tomography angiography also confirmed the absence of choroidal neovascularization, despite the presence of flat, irregular pigment epithelial detachment

areas of choroidal hyperpermeability and discrete plaque of late hyperfluorescence corresponding to type 1 neovascular tissue. In such a case, differentiating neovascular plaque over the hyperfluorescent area may be challenging. Therefore, anti-VEGF treatment was suggested as a therapeutic option to rule out the presence of CNV, especially in patients in whom vision had worsened or who were nonresponsive to treatment [15].

Another controversy about the PNV is presently debatable as to whether or not pachychoroid neovascularopathy is distinct from neovascular AMD. This is because its characteristics have yet to be well described [16]. Miyake et al. [17] investigated the phenotypic/genetic differences of PNV and neovascular AMD. Genetic susceptibility to AMD was observed to be significantly lower than genetic susceptibility to neovascular AMD in patients with pachychoroid neovascularopathy, suggesting that the two conditions are distinct clinical entities. Since pachychoroid neovascularopathy may respond differently to photodynamic therapy or anti-vascular endothelial growth factor (VEGF) therapy, it is essential that a distinction is made between pachychoroid neovascularopathy and neovascular AMD. Current multimodal imaging techniques play the major role in the process of definitive diagnosis.

Optical coherence tomography angiography (OCTA) is a novel imaging modality that provides high-quality images of the retinal and outer choroidal circulation of the choriocapillaris and retinal microvasculature without the need for intravenous dye or contrast injection [8]. OCTA was compared with FA regarding its ability to visualize CNV in a recent study. Ill-defined CNV lesions on FA, including late leakage from an undetermined source and fibrovascular PED, were shown to

be type 1 CNV on OCTA imaging [18]. The specificity of OCTA in visualizing CNV in pachychoroid spectrum diseases has also been reported in many studies. In a cross-sectional study that evaluated 27 eyes of 23 patients with chronic CSCR, FA showed CNV in 30% of the eyes, while OCTA confirmed it in all of them [8]. Quaranta-El Maftouhi et al. showed distinct CNV, not visible on ICGA imaging, in 58% of CSCR patients using OCTA [9]. Similarly, Weng et al. reported that OCTA demonstrated definite abnormal vascularization that was undetectable using other conventional imaging techniques in the outer retina in 11% of eyes with CSCR [10]. In addition, Dansingani et al. [11] identified 95% of type 1 neovascular tissue with OCTA, in contrast to dye angiography (detection rates of 18% for polypoidal lesions and 29% for CNV). However, it was suggested that the results could either be owing to the time difference between the acquisition of the dye and the OCTA imaging, or to the quiescent nature of the new vessels, resulting in the low rate of detection. However, in our study, FA, ICGA and OCTA were performed concurrently. We used OCTA and dye angiography to confirm that the proportion of PED containing neovascularization was greater than that previously estimated using dye angiography alone. The lack of disparity in time between the use of these imaging modalities enabled a direct comparison of them.

The detection of CNV is important in determining the most appropriate treatment strategy. Although pachychoroid neovascularopathy exists on the spectrum of PPE and CSCR, there is a difference in the course of the diseases and associated treatment modalities. Left untreated, CNV can cause hemorrhage, exudation, macular atrophy, and fibrosis. It

Table 2 Treatment modalities and outcomes

Patient	Baseline BCVA	Baseline choroidal thickness (μm)	Baseline vessel diameter (μm)	IV Ranibizumab	IV Aflibercept	PDT	MPL	Follow-up (month)	Final BCVA	Final Choroidal Thickness (μm)	Final Vessel Diameter (μm)
1	0.7	318	173	-	-	1	-	10	1.0	213	78
2	1.0	256	240	2	-	1	-	34	0.8	255	241
3	0.3	186	137	2	3	2	-	39	0.16	170	128
4	0.16	323	181	4	-	-	-	38	0.16	315	187
5	0.6	269	204	5	13	3	-	119	0.25	159	105
6	0.5	468	188	12	11	-	-	28	0.63	413	105
7	0.5	303	154	2	9	2	-	35	0.4	276	114
8	0.3	207	107	12	4	1	-	68	0.25	148	67
9	0.05	351	137	8	11	-	-	57	0.25	333	128
10	0.32	315	160	-	4	-	-	8	0.6	333	143
11 OD	1.0	455	344	-	-	-	-	34	0.5	453	275
11 OS	0.9	558	357	-	-	-	-	34	0.5	525	310
12	0.3	367	263	-	-	-	-	-	-	-	-
13 OD	0.2	538	275	-	2	-	-	2	-	-	-
13 OS	1.0	534	365	-	-	-	-	2	-	-	-
14	0.32	500	247	-	-	2	-	11	1	500	233
15	0.32	548	290	-	-	1	-	1	0.32	330	220
16	0.8	474	125	-	-	-	1	2	0.63	476	109
17	0.12	404	305	-	-	-	-	18	0.12	387	305

BCVA: best corrected visual acuity, IV: intravitreal, MPL: micropulse laser, PDT: photodynamic therapy

was reported in a recent study that 67% of PNV cases achieved dry macula following anti-VEGF therapy [19]. Photodynamic therapy for PCV, the last of these spectrum diseases, should also be combined with an anti-VEGF agent [20]. Therefore, the ability to recognize the true underlying pathology is essential to obtaining an optimal treatment response.

This study was limited because of its small sample size. Nevertheless, the diagnosis of PNV is frequently overlooked and this study will ensure that clinicians are aware of the appropriate diagnostic modality to use. It is likely that PNV patients have different phenotypes and treatment responses that vary from those of patients with type 1 neovascularization secondary to other causes. As a consequence, it is likely that PNV patients will follow a different natural disease course and response to treatment. Future studies that evaluate the diagnostic ability of dye angiography and OCTA in a larger series of patients are necessary to further characterize this disease and determine the optimum treatment approach.

In conclusion, this study highlights the diagnostic value of OCTA in diagnosing shallow, irregular PED seen on cross-sectional structural optical coherence tomography of the eyes with type 1 neovascularization. Conventional dye angiography may fail to show the presence of type 1 neovascularization in some cases and underestimate the presence of CNV in pachychoroid spectrum disease. OCTA may be particularly helpful in achieving an accurate diagnosis for cases with ill-defined dye angiography findings.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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