• Clinical Research •

Optical coherence tomography angiography characteristics of exudative and non-exudative treatment-naïve pachychoroid neovasculopathy

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Abstract

● **AIM:** To describe the optical coherence tomography angiography (OCTA) characteristics of exudative and non-exudative treatment-naïve pachychoroid neovasculopathy (PNV).

● **METHODS:** Thirty-five patients with exudative treatment-naïve PNV and 13 with non-exudative treatment-naïve PNV between March 2020 and December 2021 were included. All patients underwent ophthalmologic examination, including fluorescein angiography (FA), indocyanine green angiography (ICGA), spectral-domain OCT, and OCTA. The clinical data of the patients were retrospectively analyzed.

● **RESULTS:** The study included 51 eyes from 46 patients, of whom 33 (71.7%) were male. The central macular thickness (CMT) in the exudative PNV group was significantly higher than that in the non-exudative PNV group (383.97±132.16 μm *vs* 213.13±51.63 μm; *P*<0.001). The maximum height of flat irregular pigment epithelial detachments (FIPED) was 45.40±11.86 μm in the non-exudative PNV group, significantly lower than the 71.58±20.91 μm (*P*<0.001) in the exudative PNV group. The area of PNV of the non-exudative PNV group was, significantly larger than that of the exudative PNV group (1.06±0.84 mm^2 *vs* 0.63±0.80 mm^2, *P*=0.016). There was a significant difference in PNV morphology between the two groups (*P*<0.001). Multivariate logistic regression analysis found that the maximum height of FIPED (OR=1.156, 95%CI: 1.019-1.312; *P*=0.024) and microvascular branches (OR=69.412, 95%CI: 3.538-1361.844; *P*=0.005) were independent predictors of PNV activity.

● **CONCLUSION:** The OCTA imaging finds that there are significant differences in CMT, maximum height of FIPED, PNV area, and morphology of exudative PNV and non-exudative PNV groups. OCTA can accurately identify the clinical and imaging features of exudative and non-exudative treatment-naïve PNV, and distinguish PNV activity.

● **KEYWORDS:** optical coherence tomography angiography; pachychoroid neovasculopathy; type 1 choroidal neovascularization

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INTRODUCTION

Pachychoroid spectrum disease is a class of retinal choroidal disease spectrum characterized by chronic choroid thickening and choroidal vessel dilation under pathological conditions[1]. Pachychoroid neovasculopathy (PNV) is a type of pachychoroid spectrum disease with similar pathological features, such as focal or diffuse choroid thickening, Haller layer vasodilation, vascular hyperpermeability, capillary and Sattler layer atrophy, and secondary retinal pigment epithelium (RPE) injury or choroidal neovascularization (CNV)[2-3]. Traditional dye angiography provided classic detection methods for diagnosing PNV and judging the activity of the disease and effectively guided clinical treatment and follow-up. However, these traditional methods have more limitations in clinical application. The emergence of optical coherence tomography angiography (OCTA) has primarily compensated for these limitations, improving our comprehensive understanding of PNV and more accurately guiding diagnosis and treatment[4].

OCTA is a non-invasive, convenient, and fast vascular imaging technology that has recently emerged. It is an extension of optical coherence tomography (OCT) technology, which visualizes vascular morphology and blood flow changes in the retinal and choroidal layer by assessing changes in OCT signal over time. Although OCTA cannot display PNV activity due to

a lack of dye leakage, it can present abnormal visualized blood flow signals in the homogeneous background of the outer retinal or choroidal layers[5-6]. However, the absence of dye leakage on the OCTA image also benefits the analysis of PNV morphology and makes bigger differences in distinguishing PNV activity[7]. Therefore, OCTA plays a huge role in diagnosing PNV.

Although PNV has received increasing attention in recent years, few studies focused on OCTA characteristics in exudative and non-exudative treatment-naïve PNV lesions, researchers have not yet agreed on the diagnostic criteria for PNV in existing diagnostic techniques. We divided untreated patients with PNV into the exudative and non-exudative PNV groups based on the multimodal imaging characteristics of fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCT. However, whether OCTA can better describe PNV morphology remains unclear. Although some studies have found some important OCTA features that can indicate PNV activity[8-10], making a good clinical distinction is still impossible. In this study, we re-examined the clinical features of PNV from the imaging characteristics of OCTA to explore its clinical application in PNV.

SUBJECTS AND METHODS

Ethical Approval The study was conducted in agreement with the Declaration of Helsinki for human subjects' research and approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University (No. 2022-137-K-106). Informed consent was obtained from all the patients in the study.

Patients In this retrospective case series, 51 eyes of 46 patients diagnosed with exudative or non-exudative treatment-naïve PNV were enrolled from March 2020 to December 2021 in the Eye Hospital of Wenzhou Medical University.

The diagnosis of PNV was based on the presence of type 1 CNV and pachychoroid features without age-related macular degeneration (AMD) phenotypes, such as drusen or other degenerative changes. The inclusion criteria were 1) age ≥18y; 2) flat irregular pigment epithelial detachment (FIPED) defined as a flat, irregular elevation of the RPE with moderately reflective material in the sub-RPE space in either eye of the OCT B-scan; 3) type 1 CNV on OCTA, FA, and ICGA images; 4) subfoveal choroidal thickness of ≥270 μm in both eyes; 5) hypercyanescent plaque, choroidal vascular hyperpermeability and dilated choroidal vessels on ICGA images; 6) sufficiently clear ocular media to permit high-quality OCT and OCTA imaging. The exclusion criteria were 1) type 2 or 3 CNV or secondary CNV other than PNV; 2) evidence of diabetic retinopathy or any other macular or retinal vascular disease; 3) extensive subretinal fluid hampers the clear visualization of PNV morphology on OCTA; 4) any previous intervention for PNV, including photodynamic therapy (PDT), laser photocoagulation, anti-vascular endothelial growth factor (VEGF) intravitreal injection or vitrectomy.

Each enrolled patient underwent a series of comprehensive ophthalmic examinations, including best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp examination, fundus color photography (Kowa VX-20; Kowa Company Ltd, Tokyo, Japan), FA, ICGA (Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany), spectral domain OCT (SD-OCT), and OCTA (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). SD-OCT scans were performed on single high-definition vertical and horizontal lines across the foveal center with a 30° area using enhanced depth imaging mode. Twenty-five B-scans that covered an area of 20°×20° centered on the fovea were also collected. The OCTA scanning area was captured in 3×3 mm^2 or 6×6 mm^2 high-definition sections centered on the fovea. Scan size was chosen to cover the PNV lesion with retinal and choroidal vessels visible and distinguishable. Automatic real-time (ART) mode was switched on to improve the image quality, requiring a minimum of five B-scans to be averaged at each scan location. Automatic layer segmentation of OCTA image was performed by the built-in software (Heidelberg Eye Explorer, HEYEX version 1.10.2.0), and manual adjustment was selected only after reaching a consensus about segmentation inaccuracy.

Imaging Exudative PNV is defined as a flat irregular elevation of the RPE with moderately reflective material in the sub-RPE space, with intraretinal/subretinal fluid on structural OCT, ill-defined hyperfluorescent leakage or pooling of dye in late-phase on FA within PNV lesion, and corresponding hypercyanescent neovascular network in early-mid phases on ICGA. In non-exudative PNV, no signs of leakage were observed by FA and ICGA during OCTA acquisition, and no intraretinal/subretinal fluid was observed on OCT in two consecutive visits (at least 12mo apart). Considering previous studies, the assessment of OCTA images was based on the classification of CNV anatomical descriptors associated with the PNV lesion's activity[11-12]. The definitions of morphological pattern, branching, and anastomoses/loops also referred to the above studies[11-12]. The following characteristics were accepted: 1) morphological pattern, lacy wheel- or sea fan-shaped PNV lesion versus indistinct neovascular network and long filamentous linear vessels; 2) branching, obvious microvascular branches versus rare, thick, mature vessels; and 3) presence of anastomoses or loops (Figure 1). All imaging analysis and quantitative parameter measurements completed using the Heidelberg Eye Explorer software (version 1.10.2.0) were performed independently by two retina specialists (Yang C and Sun ZH). A disagreement was resolved by a senior retina specialist (Lin B).

Statistical Analysis The study used first-time measurement

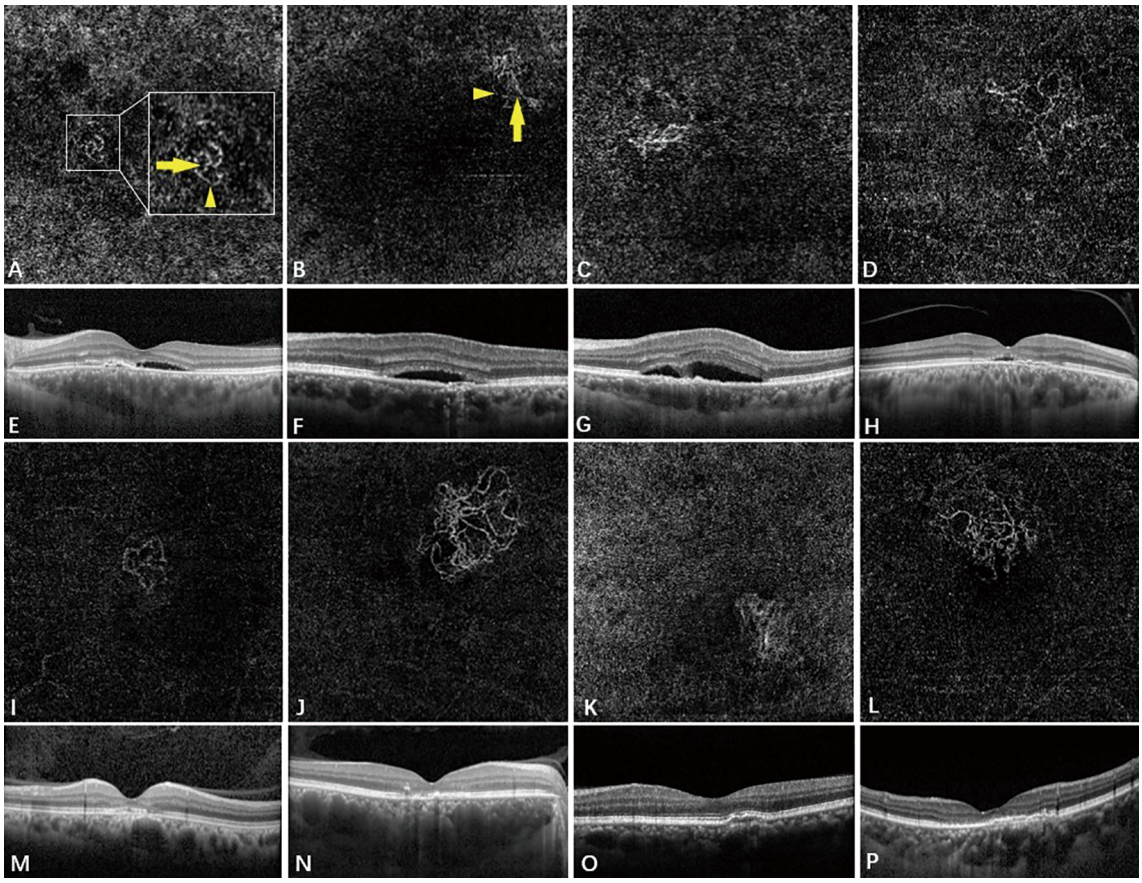

Figure 1 OCT and OCTA imaging of treatment-naïve exudative PNV (A-H) and non-exudative PNV (I-P) A, B: Lacy wheel and sea fan patterns neovascular network with obvious microvascular branches (arrowhead) and clear anastomoses/loops (arrow) in OCTA. C: The OCTA image shows the presence of an indistinct neovascular network composed of tiny vasculature in the choriocapillaris plexus layer. D: Long filamentous linear vessels with clear loops in OCTA. E-H: The OCT shows a type 1 CNV lesion, which appeared as a flat irregular pigment epithelial detachment, with sub-retinal fluid and pachychoroid. I-J: The OCTA image of non-exudative PNV appears as the lacy wheel and sea fan patterns neovascular network and is composed of thick, mature vessels with anastomoses/loops that lack microvascular branches. K-L: The OCTA images show an indistinct neovascular network and long filamentous linear vessels composed of thick, mature vessels, but microvascular branches or anastomoses/loops are absent. M-P: The OCT shows a non-exudative type 1 CNV lesion, which appeared as a flat irregular pigment epithelial detachment with pachychoroid, whereas there is no sign of intraretinal/subretinal fluid. OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; PNV: Pachychoroid neovasculopathy; CNV: Choroidal neovascularization.

data for analysis. SPSS (V.22.0, SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Data were presented as mean±standard deviation (SD) and percentages for continuous and categorical variables. Cohen's kappa coefficient was used to assess interobserver agreement for OCTA. Independent *t*-test and Mann-Whitney *U* test were used to analyze parametric and non-parametric datasets, respectively. Chi-square or Fisher exact test was used to compare categorical variables. Multivariate logistic regression analysis assessed the risk factors associated with PNV activity, and correlation between independent variables was used to test collinearity. The odds ratio (OR) and 95% confidence interval (CI) were calculated. A two-tailed *P*-value of <0.05 was accepted as a statistically significant difference or correlation.

RESULTS

Study Population and Pachychoroid Neovasculopathy Features

We enrolled 51 eyes of 46 patients with treatment-naïve PNV. Of these, 33 patients (71.7%) were male; the mean age was 53.65±8.05y (range 35-69y). The age of diagnosis was statistically significantly different between male and female patients with PNV. The mean BCVA of the included eyes was 0.36±0.28 logMAR (range, 0-1.40 logMAR). Exudative PNV was found in 36 eyes of 35 patients, and non-exudative PNV was identified in 15 eyes of 13 patients. Notably, there were two cases where each patient's eyes were allocated to different groups. No statistical differences were found in terms of age, BCVA, history of hypertension, and previous central serous chorioretinopathy (CSC) between the two groups (*P*=0.784, 0.184, 0.265, and 0.070, respectively; Table 1).

Interobserver Agreement of OCTA

The interobserver agreement for OCTA descriptive parameters including lacy-wheel/sea-fan, indistinct, filamentous, microvascular

Table 1 Baseline demographic characteristics

Parameters	Total PNV	Exudative PNV	Non-exudative PNV	*P*
No. of patients (No. of eyes)	46 (51)	35 (36)	13 (15)	-
Age (range), y	53.65±8.05 (35-69)	53.44±8.29 (36-69)	54.13±7.69 (35-65)	0.784
Male, *n* (%)	33 (71.7)	25 (71.4)	10 (76.9)	0.988
Right/left	20/31	14/22	6/9	-
BCVA (range), logMAR	0.36±0.28 (0-1.40)	0.39±0.28 (0.05-1.40)	0.29±0.29 (0-1.00)	0.184
Hypertension, *n* (%)	14 (27.5)	12 (38.9)	2 (14.3)	0.265
Previous CSC, *n* (%)	31 (60.8)	19 (52.8)	12 (80.0)	0.07

PNV: Pachychoroid neovasculopathy; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CSC: Central serous chorioretinopathy.

Table 2 OCT and OCTA characters in exudative PNV and non-exudative PNV

Parameters	Exudative PNV	Non-exudative PNV	*P*
No. of eyes	36	15	-
Fovea involvement	17 (47.2)	11 (73.3)	0.088
CMT, μm	383.97±132.16	213.13±51.63	<0.001
SFCT, μm	370.94±70.83	392.33±93.81	0.381
Max width of FIPED, μm	1486.06±637.35	1484.67±633.22	0.992
Max height of FIPED, μm	71.58±20.91	45.40±11.86	<0.001
Area of PNV, mm^2	0.63±0.80	1.06±0.84	0.016
Morphological pattern of PNV			<0.001
Lacy-wheel/sea-fan	31 (86.1)	5 (33.3)	0.001
Indistinct	4 (11.1)	4 (26.7)	0.213
Filamentous	1 (2.8)	6 (40.0)	0.002
Microvascular branches	31 (86.1)	1 (6.7)	<0.001
Anastomoses/loops	34 (94.4)	7 (46.6)	<0.001

SFCT: Subfoveal choroidal thickness; CMT: Central macular thickness; FIPED: Flat irregular pigment epithelial detachments; Max: maximum; PNV: Pachychoroid neovasculopathy.

branches, and anastomoses/loops were very good, with kappa values of 0.902, 0.865, 0.922, 0.870 and 0.852, respectively (*P*<0.001).

Characteristics of Exudative and Non-Exudative PNV of OCT and OCTA Imaging The comparison of characteristics between the OCT and OCTA groups was shown in Table 2. Compared with the exudative PNV group, the non-exudative PNV group had more foveal lesions, but the difference was not statistically significant.

OCT imaging revealed that the central macular thickness (CMT) in the exudative PNV group was significantly greater than that in the non-exudative PNV group (383.97±132.16 μm *vs* 213.13±51.63 μm; *P*<0.001). The maximum height of FIPED was significantly greater in the eyes with exudative PNV than in those with non-exudative PNV (71.58±20.91 μm *vs* 45.40±11.86 μm; *P*<0.001). The subfoveal choroidal thickness or maximum width of FIPED was not significantly different between the two groups (Table 2).

The OCTA imaging results showed that the PNV area in the exudative PNV group was significantly smaller than that in the non-exudative PNV group (0.63±0.80 mm^2 *vs* 1.06±0.84 mm^2; *P*=0.016). There was a significant difference in PNV morphology patterns between exudative and non-exudative PNV groups (*P*<0.001; Figure 1, Table 2). Lacy wheel and sea fan patterns were observed in 36 eyes, with 31 (86.1%) in the exudative and 5 (33.3%) in the non-exudative PNV group. However, the filamentous pattern was found in 7 eyes, with 1 (2.8%) in the exudative and 6 (40.0%) in the non-exudative PNV group. Microvascular branches were identified in 32 eyes, with 31 (86.1%) in the exudative and 1 (6.7%) in the non-exudative PNV group (*P*<0.001). Anastomoses or loops were identified in 41 eyes, with 34 (94.4%) in the exudative and 7 (46.6%) in the non-exudative PNV groups, respectively (*P*<0.001; Table 2).

Assessment of Risk Factors for PNV Activity Risk factors for PNV activity were assessed using a logistic regression model. After adjusting for confounding factors, multivariate logistic regression analysis found that the maximum height

Table 3 Multivariate logistic regression analysis of risk factors of exudative PNV

Variables	Univariate		Multivariate	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Max height of FIPED	1.138 (1.057-1.224)	0.001	1.156 (1.019-1.312)	0.024
Microvascular branches	86.8 (9.260-813.606)	<0.0001	69.412 (3.538-1361.844)	0.005
Area of PNV	0.545 (0.263-1.127)	0.102	0.35 (0.061-2.016)	0.24

FIPED: Flat irregular pigment epithelial detachments; Max: Maximum; PNV: Pachychoroid neovasculopathy.

of FIPED (cut-off=51 μm, OR=1.156, 95%CI: 1.019-1.312; *P*=0.024) and microvascular branches (OR=69.412, 95%CI: 3.538-1361.844; *P*=0.005) significantly increased the possibility of PNV activity (Table 3). After conducting receiver operating characteristic analysis, the area under the curve of both parameters was 0.981 (95%CI: 0.896-1.000; *P*<0.001).

DISCUSSION

Currently, there is a paucity of studies analyzing the OCTA characteristics of exudative and non-exudative treatment-naïve PNVs. Additionally, existing studies suffer from small sample sizes and limited reporting of PNV morphology, specifically focusing on tangled filamentous vascular networks[8,13]. Therefore, this study aims to describe the OCTA characteristics of treatment-naïve PNV, including 36 eyes with exudative treatment-naïve PNV and 15 eyes with non-exudative treatment-naïve PNV. This study will contribute to a deeper understanding of the pathogenesis, pathological changes, and clinical manifestations of PNV. The study indicated that the CMT of the exudative PNV group was significantly higher than that of the non-exudative PNV group. The maximum height of FIPED of the non-exudative PNV group was significantly lower than that of the exudative PNV group. There was a significant difference in PNV morphology between the two groups.

In our study, we also found that the BCVA did not exhibit a statistically significant difference between the two groups, which contrasts with the findings of previous studies. Lee *et al*[9] reported that non-exudative PNV had superior visual acuity to exudative PNV at baseline. This discrepancy may be attributed to the inclusion of treatment-naïve PNV patients in our study, who were relatively younger and had a smaller area of baseline CNV. In our study, the en-face OCTA image of exudative PNV revealed a greater prevalence of lacy wheel- and sea fan-shaped CNV lesions, which exhibited numerous microvascular branches that anastomose with one another. Azar *et al*[8] found that OCTA revealed a network of tangled filamentous vessels in all eyes with PNV, which was similar to the findings of our study. However, in our study, the en-face OCTA image of non-exudative PNV exhibited an indistinct neovascular network or long filamentous linear vessels, comprised of thick, mature vessels lacking microvascular branches or anastomoses/loops. Additionally, we also observed lacy wheel and sea fan PNVs without microvascular branches in the non-exudative PNV group. These observations suggest that non-exudative PNV possesses distinctive OCTA imaging characteristics that have not been previously described, leading to marginally divergent outcomes. In contrast, exudative PNV exhibited type 1 CNV with smaller areas, but greater numbers of microvascular branches and anastomoses/loops. This difference in pathological processes may explain the distinct growth patterns observed between the two PNV groups. In exudative PNV, the CNV consists of immature and tiny vessels in the early stages of development, making it prone to exudation. On the other hand, non-exudative PNV primarily comprises mature and thick vessels, with more intact vascular endothelial cells that are less likely to cause exudation. These vessels tend to remain stable for an extended period, resulting in a larger CNV area when detected. Previous studies have not measured the height and width of the FIPED in both exudative and non-exudative PNVs. In this study, we found that the maximum height of the FIPED in non-exudative PNV was lower than that of exudative PNV. The height of the lesion was found to be closely related to its activity. In multivariate logistic regression analysis, the maximum height of FIPED and the presence of microvascular branches were independent factors that distinguished between exudative and non-exudative PNVs. These findings suggest that OCTA has the potential to serve as a reliable tool for the early detection, morphological examination, treatment, and monitoring of PNVs.

Recently, OCTA has been widely used in clinical practice as a revolutionary breakthrough in fundus imaging. Because of its non-invasive and convenient operation, it can partially replace traditional dye angiography and has advantages over traditional dye angiography in some cases[3,10]. It has also played a critical role in diagnosing CNV and evaluating the efficacy of anti-VEGF therapy[14]. Studies have demonstrated a good correspondence between OCTA and FA in diagnosing CNV[15]. Moreover, OCTA was highly reliable in diagnosing CNV. It can objectively evaluate the dynamic changes of CNV and provide a reliable basis for subsequent treatment[16]. While FA and ICGA are considered the classic methods for determining the activity of PNV, they are invasive, time-consuming, and carry the risks of allergies, limiting their suitability for follow-up purposes. A prospective cross-sectional study suggests that multimodal imaging using a combination of OCTA, OCT line

scanning, and dye angiography can serve as the gold standard for diagnosing CNV in CSC patients[17].

By utilizing efficient and non-invasive OCTA to observe PNV, we have identified significant differences in the morphology of exudative and non-exudative PNVs. Notably, the presence of an indistinct neovascular network or long filamentous linear vessels is more commonly associated with non-exudative PNV. Previous studies have also indicated that non-exudative PNV was more likely to progress to polypoid choroidal vasculopathy (PCV)[9]. In our study with a 12-month follow-up, none of the eyes in the non-exudative PNV group developed exudation or progressed to PCV, while two eyes in the exudative PNV group progressed to PCV. These findings suggested that non-exudative PNV lesions in these patients may remain stable for an extended period, reducing the need for excessive anti-VEGF therapy. This can assist retina specialists in making informed decisions, potentially leading to extended follow-up periods, and alleviating the social and economic burdens on patients.

Clinically, CNVs were commonly identified in types 1 and 2. In the case of type 1 CNV, Costanzo *et al*[18] found that OCTA could provide both quantitative and qualitative information, making it a valuable tool for assessing neovascular lesions and therapeutic responses. Ameen *et al*[19] observed that type 2 CNV typically exhibited a glomerular or medusa shape with surrounding dark halos on OCTA. However, specificity still needs to be further explored. OCTA is a relatively simple and flexible tool for retina specialists to identify CNV[20]. Differences in OCT and OCTA have been observed between exudative and non-exudative type 1 CNVs of PNV in our study, as well as possible differences in ocular symptoms. Therefore, OCTA serves as an important diagnostic tool for retinal choroidal vasculopathy, providing a novel approach for identifying specific types of PNV associated with type 1 CNV.

This study is subject to several limitations. First, its single-center nature restricted the generalizability of the findings. Secondly, the retrospective design introduced the possibility of selection bias influencing the results. To comprehensively evaluate alterations in various indicators of exudative PNV pre- and post-anti-VEGF treatment, prospective studies are required. Furthermore, considering the relatively lower incidence of non-exudative PNV compared to exudative PNV, future studies with larger patient cohorts and longer follow-up periods are necessary. It is also important to acknowledge that this study exclusively included treatment-naïve PNV eyes, which may lead to differing outcomes compared to prior research. Lastly, the limited number of cases examined in this study represents an additional limitation.

In conclusion, the OCTA imaging revealed notable variations in the CMT, the maximum height of FIPED, the area of PNV, and the morphology of the exudative and non-exudative treatment-naïve PNV. OCTA is a non-invasive and effective approach that identifies the clinical features and imaging characteristics of exudative and non-exudative treatment-naïve PNV, allowing for the distinction of PNV activity. Moreover, OCTA aids retina specialists in gaining a better understanding of PNV, formulating treatment strategies, and predicting the prognosis of PNV patients, thereby preventing the onset and progression of the disease.

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