• Clinical Research •

Analysis of choroidal morphology and comparison of imaging findings of subtypes of polypoidal choroidal vasculopathy: a new classification system

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Abstract

● **AIM:** To classify polypoidal choroidal vasculopathy (PCV) into 2 subtypes based on the subfoveal choroidal thickness (SFCT) and to further evaluate their multimodal image features.

● **METHODS:** A retrospective observational case series study. Sixty-four eyes of 64 patients with PCV were enrolled and classified into 2 groups based on SFCT (thick-choroid group/thin-choroid group). Then further analyze the spectrum domain optical coherence tomography (SD-OCT) and indocyanine green angiography (ICGA) differences of the two subtypes. Imaging analysis included measurement of SFCT, maximum vascular diameter ratio (MVDR), choroidal vascularity index (CVI), central macular thickness (CMT), and the presence of pigment epithelial detachment (PED) on SD-OCT. Polypoidal lesions (polyps) number, branching vascular network (BVN) area, greatest linear dimension (GLD), and the choroidal vascular hyperpermeability (CVH) were analyzed by ICGA.

● **RESULTS:** The distribution of SFCT was bimodal with two peaks at 195 and 285 μm, and a trough at 225 μm. The 225 μm was taken as the cutoff point for the following classification of thick/thin choroid groups. The PCV eyes in the thick-choroid group presented with greater MVDR, CVI within 3 and 6 mm of the fovea, but lower CMT, less PED, small PED diameters on SD-OCT scans, and fewer polyps, smaller BVN and GLD, but more frequency of CVH on ICGA.

● **CONCLUSION:** The SFCT at 225 μm can be used as a readily available indicator for the classification of PCV subtypes. The thick-choroid group presents much apparent enlargement of the choroidal layer and vasculature expansion, which indicates different pathogenesis of the two subtypes.

● **KEYWORDS:** polypoidal choroidal vasculopathy; spectral-domain optical coherence tomography; indocyanine green angiography; subfoveal choroidal thickness
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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi *et al*[1] in 1990 as a new entity, detected and defined by its indocyanine green angiography (ICGA) appearance characterized by polypoidal lesions (polyps) and branching vascular network (BVN). It has a high prevalence in Asian population of age-related macular degeneration (AMD) with the ratio of 10%-54%[2-3]. The pathogenesis of PCV remains controversial, particularly regarding whether PCV is a variant of neovascular AMD (nAMD), especially type 1 choroidal neovascularization (CNV), or a distinct clinical entity[4-9]. Yuzawa *et al*[10] reported that PCV is caused by inner choroidal vessel abnormalities, instead of CNV, and further classified the disease into 2 types: typical PCV and polypoidal CNV according to their different features on ICGA. Some researchers classify PCV into 2 subtypes according to ICGA and optical coherence tomography (OCT) findings and reported the existence of two distinct types of PCV[11]. Type 1 represents CNV, while type 2 involves choroidal vasculature abnormalities.

The development of spectrum domain optical coherence tomography (SD-OCT), especially the introduction of

enhanced depth imaging (EDI)-OCT to the study of PCV makes it possible for the investigation of the choroidal morphology and blood flow characteristics of the disease. Recently, the importance of thick choroid (pachychoroid) in PCV led some investigators to suggest PCV falls within the pachychoroid spectrum of conditions that may have a different cause from AMD[12]. Subsequent studies also proved that choroidal thickness increased in eyes with PCV[13-15]. But the value varies a lot. Lee *et al*[15] reported there was a bimodal distribution of PCV eyes with two peaks at different subfoveal choroidal thickness (SFCT) levels, suggesting that two subtypes of PCV exist, with either pachychoroid or nonpachychoroid features. Other recent studies have produced similar results and further proved that the different phenotype presented different responses to treatment[11,15-16].

Although the term pachychoroid was originally conceived to reflect choroidal thickening, new information has broadened its original description to emphasize additional qualitative features, including diffuse choroidal thickening or vessel expansion localized within the disease focus and attenuation of choriocapillaris overlying pachyvessels bring them closer to the Bruch-retinal pigment epithelium (RPE) complex[17-19].

In this study, we envisage to clarify PCV eyes into 2 phenotypes based on SFCT, and further explore their differences of multi-model imaging characteristics.

SUBJECTS AND METHODS

Ethical Approval This retrospective cohort study was approved by the Institutional Review Board at Peking Union Medical College Hospital (S-K561) and followed the principles of the Declaration of Helsinki. The informed consent was obtained from all subjects.

Patients' Enrollment This study was a retrospective, observational case series of 64 consecutive treatment-naive patients diagnosed with PCV at Peking Union Medical College Hospital from July 2015 to December 2017. The inclusion criteria were: 1) diagnosed with PCV confirmed by ICGA; 2) refractive errors ranged from -6.0 to +3.0 diopters; 3) for patients with bilateral eye involved, only one random eye was enrolled. The exclusion criteria included 1) with a previous history of treatment like photodynamic therapy or anti-vascular endothelial growth factor (VEGF) therapy; 2) associated with other macular or eye diseases, such as AMD, significant cataracts, glaucoma, uveitis, or any other associated retinal vascular diseases; 3) ocular surgery or trauma; 4) cloudy refracting media that the images were insufficient enough for assessment.

Ophthalmic Examinations All patients underwent a comprehensive ophthalmic examination including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, color fundus photograph (TRC-50DX, Topcon, Japan), fluorescein angiography (FA), ICGA, and SD-OCT with EDI mode (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). SD-OCT images were obtained using a standard imaging protocol consisting of 49 B-scans spanning a 20×20° frame, along the horizontal planes through the foveal center. The contralateral eye status was assessed through color fundus photography by 2 investigators and labeled with normal, PCV, drusen or nAMD.

ICGA and SD-OCT Analysis ICGA parameters included polyps' number, BVN area, greatest linear dimension (GLD) and choroidal vascular hyperpermeability (CVH) of the lesion. The GLD was defined as the greatest distance enclosed by BVN and polyps perimeter. The CVH was defined as multifocal area of hyperfluorescence with blurred margins. Polyps' number, BVN area were assessed at the early and middle stage (0-15min), while GLD and CVH were assessed and measured at the middle and late stage (15-30min) using the built-in tool of ICGA.

SD-OCT parameters included SFCT, central macular thickness (CMT), maximum vascular diameter ratio (MVDR), choroidal vascularity index (CVI) within 3 and 6 mm diameter centralized by the foveal, and the height and diameter of pigment epithelium detachment (PED). SFCT, CMT, MVDR, and the height and diameter of PED were measured using the built-in measuring tool. SFCT was measured vertically from the outer surface of the RPE to the choroidal-scleral interface from fovea scans. The CMT was calculated automatically by the SD-OCT instrument. The MVDR was defined as the ratio of vertical maximum choroidal vascular diameter and the whole choroid thickness in the same position. PED height and diameter were measured as the maximum distance from the PED top to the RPE layer and the maximum distance from the two ends of the PED lesions. CVI were calculated according to the version of the protocol described by Sonoda *et al*[20]. The OCT image with EDI mode was analyzed by Image J software (version 1.51; http://imagej.nih.gov/ij/) in the regimens of 3 and 6 mm diameter centralized by the foveal respectively.

The counting of polyps' number, measurement of BVN area, assessment of GLD and CVH were accomplished by 2 independent observers (Liu ZY and Xia S). SFCT, MVDR, choroidal thickness differential ratio (CTDR), the PED height and diameter were measured by another 2 observers (Li B and Li DH) and the values were averaged to obtain the reported results. An experienced retina specialist (Chen YX) was invited for estimation for contradictions in this study.

Statistical Analysis SPSS 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used as the statistical analysis software for the assessments performed in this study. For continuous variables, independent samples *t*-test was performed if the data followed the normal distribution,

otherwise Mann-Whitney *U* test were performed for the data compare between the two groups. The χ^2 tests were used for categorical variables' comparison. A *P* value <0.05 was considered to be statistically significant. Spearman correlation analysis was performed on for the continuous variable of abnormal distributions.

RESULTS

Sixty-four eyes from 64 patients with PCV were enrolled, with a mean age of 64.0±7.5 years old. Seven of them were bilateral involved. Other demographic information and ophthalmic examinations were listed in Table 1. The patients of the thick choroid group were much younger than those in thin choroid group.

The mean SFCT of the 64 eyes enrolled was 233.2±80.7 (84-412) μm. The frequency distribution of SFCT presents a bimodal pattern with 2 peaks at 195 and 285 μm, and a trough at 210-240 μm (Figure 1). We choose the median value of this SFCT interval scale at 225 μm as the cutoff point and divided the study eyes into two groups: the thick-choroid (SFCT>225 μm) and thin-choroid (SFCT<225 μm) groups. The ICGA and SD-OCT features of the 2 groups were listed in Table 1.

The PCV eyes in the thick-choroid group presented younger age and better BCVA with fewer polyps, smaller BVN area and GLD, and a higher proportion of CVH on ICGA. On SD-OCT scan, they showed a lower CMT but higher MVDR and CVI. PED is less frequently presented and much smaller than those in thin choroid group. We further explored the correlation of SFCT and other image parameters and found it strongly correlated with CVI and CVH, and moderately correlated with MVDR and BVN area (Table 2). Figures 2, 3 show the multimodal image of PCV cases of the two groups respectively.

Table 1 Demographic and image features of the 2 groups divided by SFCT *n* (%)

Parameters	Thick choroid group (*n*=31)	Thin choroid group (*n*=33)	*P*
Age (y)	60.23±5.96	67.48±7.35	<0.001[a]
Gender (male)	20 (64.5)	20 (60.6)	0.747
Fellow eye status			0.677
Normal	21 (67.7)	19 (57.6)	
PCV	3 (9.7)	4 (12.1)	
nAMD	0	2 (6.1)	
Drusen	7 (22.6)	7 (21.2)	
BCVA (logMAR)	0.58 (0.28)	0.86 (0.43)	<0.001[a]
Axial lengths (mm)	23.18±0.51	23.42±0.73	0.139
ICGA parameters			
Polyps number (*n*)	1.81±1.06	3.12±1.49	<0.001[a]
BVN area (mm²)	3.24±2.00	5.86±3.03	<0.001[a]
GLD (μm)	2405.8±655.7	3235.7±1135.4	0.003[a]
CVH	24 (77.4)	4 (12.1)	<0.001[a]
SD-OCT parameters			
CMT (μm)	371.9±77.4	452.4±165.2	0.048[a]
SFCT (μm)	304.3±47.7	166.5±36.1	<0.001[a]
MVDR	0.71±0.08	0.65±0.06	0.02[a]
CVI			
φ=3 mm	0.62±0.04	0.53±0.04	<0.001[a]
φ=6 mm	0.63±0.04	0.52±0.04	<0.001[a]
PED			
Presence	18 (58.1)	27 (81.8)	0.038[a]
Height (μm)	314.0±120.7	339.0±176.8	0.982
Diameter (μm)	1497.9±379.8	2553.4±1555.6	0.022[a]

PCV: Polypoidal choroidal vasculopathy; nAMD: Neovascular age-related macular degeneration; BCVA: Best-corrected visual acuity; ICGA: Indocyanine green angiographic; BVN: Branching vascular network; GLD: Greatest linear dimension; CVH: Choroidal vascular hyperpermeability; SD-OCT: Spectrum domain optical coherence tomography; CMT: Central macular thickness; SFCT: Subfoveal choroidal thickness; MVDR: Maximum vascular diameter ratio; CVI: Choroidal vascularity index; PED: Pigment epithelial detachment. [a]Statistically significant.

DISCUSSION

In this study, we explored the SFCT in PCV eyes and found it a bimodal pattern frequency distribution similar to some previous studies[15-16,21], while the values of the peaks and the trough are slightly different from other studies. There have been some reports supporting the idea that PCV could be further classified into 2 subgroups with different pathogenesis. Type 1 PCV is presumed to derive from the primary abnormalities of the choroidal vasculature, and type 2 PCV is associated with CNV. We also proved that the thick-choroid PCV group presented a significant higher proportion of CVH, greater MVDR and CVI, the parameters indicating the present of pachychoroid and implying the aetiological differences between the two groups that differ by choroidal characteristics. The thick-choroid group also presented a clinical feature of better BCVA and younger age, which agrees with the study of Chang and Cheng[16] that this presented some central serous chorioretinopathy (CSC)-like features.

CVI is the ratio of the choroidal blood vessel luminal area (LA) to total choroidal area (TCA) within a specified subfoveal area, measured by OCT images, and was proposed as a novel tool to describe choroidal vasculature[20,22]. CVI is considered to be a better indicator comparing with SFCT since it is not affected by age variation and has been widely used to evaluate choroidal vascular diseases, such as exudative AMD, CSC and Vogt-Koyanagi-Harada disease. Resent studies have proved that eyes with nAMD demonstrated reduced CVI but insignificant differences in choroidal thickness compared with their fellow eyes. This parameter is also demonstrated to correlate with CVH in PCV eyes. In our study, the CVI

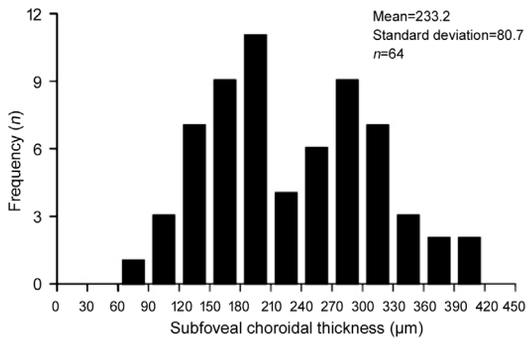

Figure 1 The bimodal frequency distribution of the SFCT with two peaks at 195 and 285 μm and a trough at 225 μm.

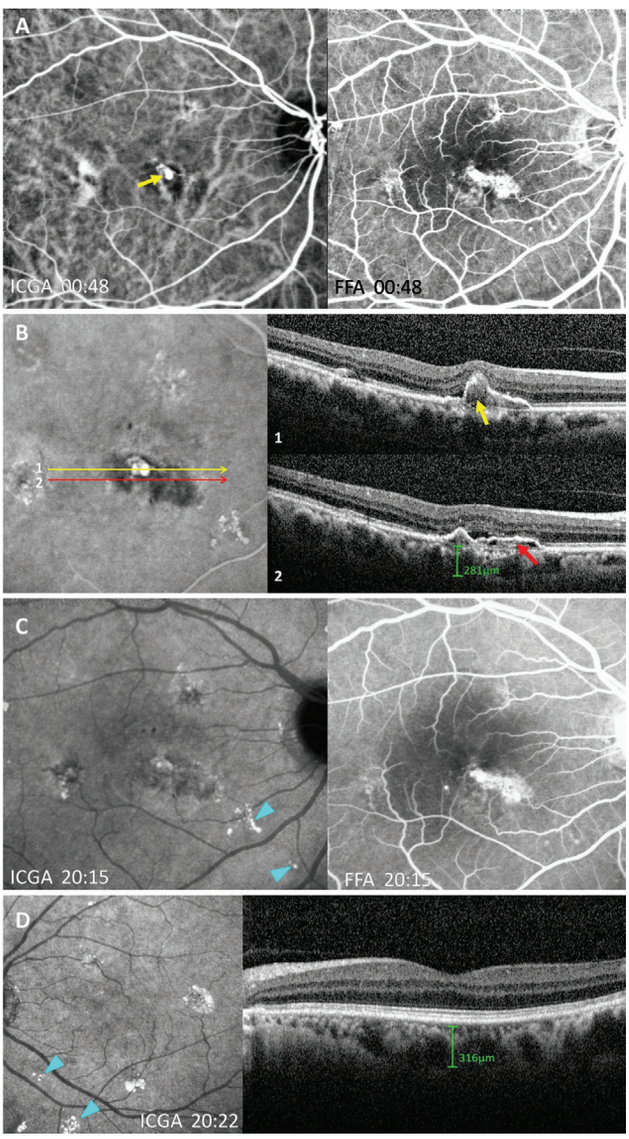

Figure 2 PCV case in thick-choroid group: multimodal image of a 62-year-old male A: Polypoidal lesion and relatively focal BVN (yellow arrow) at the fovea at the early stage of ICGA. FFA presented a dying leakage at the corresponding area. B: SD-OCT shows a steep PED and a notch beneath correspond to polyps (yellow arrow). Double layer sign beside PED correspond to the location of BVN. Choroid thicken with a SFCT reach 281 μm with choroidalcapillary atrophy. C: CVH is presented at the late stage of ICGA as dot-like high fluorescence (blue arrow head). D: The contralateral eye also presented CVH (blue arrow head); SFCT measured on SD-OCT is 316 μm.

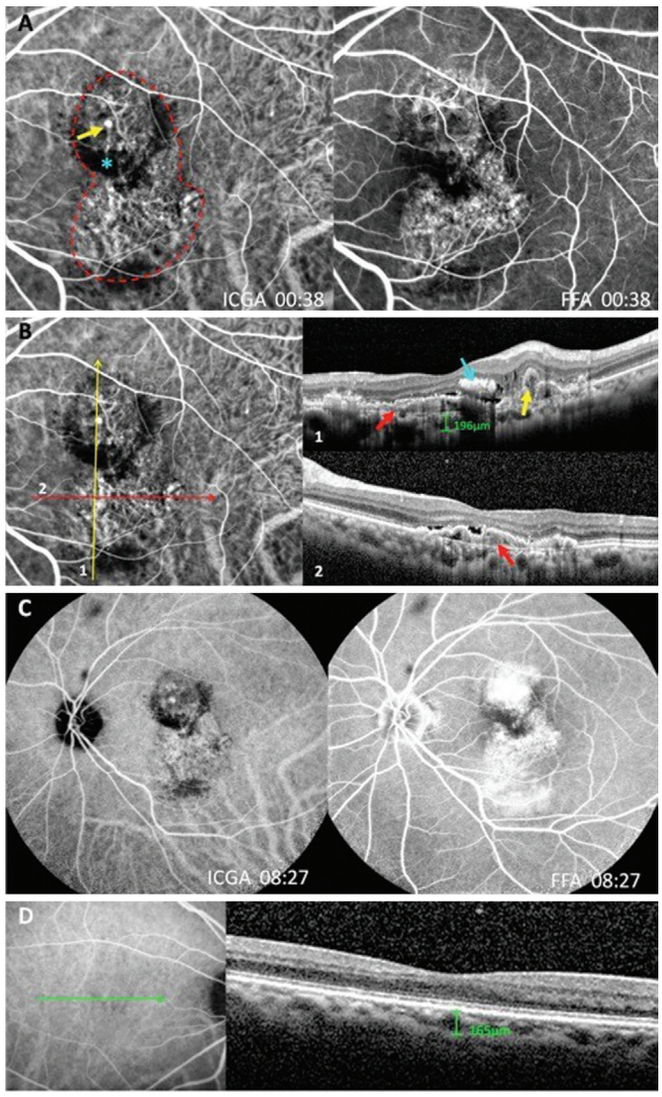

Figure 3 PCV case in thin-choroid group: multimodal image of a 69-year-old female A: Polypoidal lesion (yellow arrow) and umbrella BVN (red dot line) at the early stage of ICGA with subretinal hemorrhagic hypo fluorescence (blue asterisk). FFA presented a dying leakage at the corresponding area of polyps and BVN. B: SD-OCT shows thumb-like bulge of PED (yellow arrow) corresponding to the polypoidal lesion accompanied by retinal hemorrhage (blue arrow). The double layer sign indicates the locateon of BVN (red arrow). The SFCT was 196 μm without apparent choroidalcapillary atrophy. C: Non CVH was presented at the late stage of ICGA. D: The contralateral eye also doesn't presented character of CVH; SFCT measured on SD-OCT is 165 μm.

results of thick-choroid PCV group was similar to other studies on PCV eyes, and that of the thin choroid group is similar to AMD group which also supported the existence of 2 PCV subtypes with different pathogenesis[23-24]. In addition, the thick-choroid group also presented higher MVDR indicating that choroid thickens in the thick choroid-group with relatively higher vascular density and dilatation of the outer choroidal vessels. Furthermore we found the CVI within 6 and 3 mm diameter presented no significant differences and correlated

Table 2 Correlation analysis of SFCT and other SD-OCT and ICGA parameters

Parameters	SFCT	
	R	*P*
SD-OCT parameters		
CMT	-0.237	0.059
CVI		
φ=3 mm	0.735[a]	<0.001
φ=6 mm	0.729[a]	<0.001
MVDR	0.366[a]	0.003
PED (*n*=43)		
Height	-0.242	0.462
Diameter	0.075	0.633
ICGA parameters		
Polyps number	-0.384[a]	0.002
BVN area	-0.354[a]	0.004
GLD	-0.282[a]	0.024
CVH	0.576[a]	<0.001

SD-OCT: Spectrum domain optical coherence tomography; CMT: Central macular thickness; SFCT: Subfoveal choroidal thickness; MVDR: Maximum vascular diameter ratio; CVI: Choroidal vascularity index; PED: Pigment epithelial detachment; ICGA: Indocyanine green angiographic; BVN: Branching vascular network; GLD: Greatest linear dimension, CVH: Choroidal vascular hyperpermeability. [a]Correlation is significant at the 0.01 level.

with SFCT, which could be measured easily on SD-OCT images through a built-in tool. Some studies expressed concern over whether it could represent the status of pachychoroid, which refers to the dilation of the large vessels and atrophy of the choroidalcapillary layers in addition to the increase of the choroid thickness. However, we found in this cohort of PCV eyes, the SFCT correlated with CVI and CVH, which had been proved to be reliable indicators for the estimation of pachychoroid. Considering its readily availability, SFCT could be considered a potential parameter for PCV classification.

Beside of the vasculatures difference between the 2 groups, we also found the thick-choroid group with fewer polyps' number, smaller BVN area and GLD, but lower CMT, less and smaller PED. We hypothesis this phenomenon also indicates a specific origin of the two groups. Previous studies reported a relatively local spread of BVN comparing with type 1 CNV accords with our study[25]. With the original abnormality from the choroid, the polyps presented with more complicated hemodynamics and higher flow velocity and diffused increased fluid pressure, which may lead to subretinal fluid and PED within the 6 mm diameter of the fovea. These specific characteristics result in visual symptoms and drive the patients for consultation earlier before they grow large enough as those in the thin-choroid group. Some previous studies also proved that the polyps mostly set beneath the peak of the PED in type 1 PCV while those laydown between RPE and the Bruch's membrane in the type 2 subtype[26-27]. Also the polyps in type 1 PCV is less frequently presented in optical coherence tomography angiography (OCTA) comparing with type 2 PCV eyes, which was mostly explained by the unstable flow status and the location variation of the polyps in type 1 PCV[27]. These studies could some kind support the hypothesis about the correlation between polyps' number and BVN and GLD area. However, it still needs more demonstration and further studies.

There are also some limitations in this study. First, the sample size is relatively small. Studies with more patients will help find a more precise cutoff point of SFCT in Chinese people. Second, since this is a retrospective case series study, we couldn't further explain the difference this 2 groups on treatment and follow up.

In conclusion, in this study, we provide a new classification system of PCV according to SFCT at 225 μm. And found significant different image features between the thick- and thin-choroid groups, which verified the scientificity, both in statistical and ophthalmic perspectives. It is also more readily available comparing with previous classification system. The different characters of the two groups also indicate a different pathogenesis of different PCV subtypes.

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