Polypoidal Choroidal Vasculopathy: Perspective from Noninvasive Retinal Imaging

Clinical differentiation between PCV and typical neovascular AMD is important, as these 2 diseases differ in natural course and response to treatment.

BY HIDEKI KOIZUMI, MD, PhD

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (AMD) characterized by multiple recurrent serosanguineous detachments of the retinal pigment epithelium (RPE) and neurosensory retina secondary to leakage and bleeding from choroidal vascular lesions. Indocyanine green angiography (ICGA) reveals the branching choroidal vascular networks that terminate in polypoidal dilations, and these 2 components are known to be characteristic findings in PCV. Precise pathogenesis of PCV has yet to be clearly elucidated and is a subject that remains controversial. It is important, however, to clinically differentiate between PCV and typical neovascular AMD because these 2 entities show different natural courses and responses to treatments.

Recent developments in retinal imaging, such as enhanced-depth imaging optical coherence tomography (EDI-OCT) and fundus autofluorescence (FAF) photography, have provided some perspective on PCV. This article introduces up-to-date findings by means of these relatively new imaging methods for further understanding of the pathologic mechanisms of PCV.

EDI-OCT FINDINGS IN PCV

We performed EDI-OCT on consecutive eyes with PCV and typical neovascular AMD and showed that PCV eyes demonstrated significantly greater mean subfoveal choroidal thickness (293 μm) than typical neovascular AMD eyes (245 μm; Figure 1). Other groups have also reported comparable results. Therefore, we concluded that the choroidal vascular lesion seen in PCV may not be just choroidal neovascularization (CNV) accompanied by saccular capillary dilations at the border, but may have a significant structural difference in the choroid compared with typical neovascular AMD.

Figure 1. EDI-OCT comparison between typical neovascular AMD and PCV. In these cases, subfoveal choroidal thickness (double-headed arrows) was 160 μm in typical neovascular AMD (A) and 342 μm in PCV (B). Arrows indicate the inner surface of the sclera.
Why does PCV have thicker choroid compared with typical neovascular AMD? The reason may be partially attributed to the dilation of middle or large choroidal vessels or choroidal vascular hyperpermeability (CVH) revealed by ICGA. CVH, which is visualized as multifocal hyperfluorescence in the middle and late phases of ICGA, usually bilaterally, was originally described as a characteristic finding in central serous chorioretinopathy (CSC). Sasahara and associates reported that PCV eyes demonstrated CVH with significantly higher frequency (9.8%) than typical neovascular AMD eyes (1.9%). In our study, 34.7% of PCV eyes demonstrated CVH. Other recent studies also reported comparable frequencies of 59.3% and 30.8%. The reason why our findings and those of others showed a higher frequency of detected CVH than did the findings of Sasahara’s group remains unknown; however, it might be that, at least in our study, we routinely took ICGA angiograms in the macula and periphery for all involved cases. As expected, PCV eyes with CVH showed greater mean subfoveal choroidal thickness (339 μm) than those without CVH (225 μm; Figures 2 and 3), probably due to the increased hydrostatic pressure within the choroid. Therefore, the presence of CVH was found to be 1 of the important determinants for the choroidal thickening seen in PCV.

**CLINICAL SIGNIFICANCE OF CHOROIDAL VASCULAR HYPERPERMEABILITY IN PCV**

As mentioned above, PCV eyes with CVH demonstrated greater subfoveal choroidal thickness than those without CVH. Thus, one can assume that CVH may be related to the pathogenesis of PCV to a certain degree.

To more clearly define this relationship, we performed a study looking at the clinical characteristics of PCV and CVH. In addition to the thickened choroid, PCV cases with CVH were found to more frequently demonstrate bilateral occurrence of neovascular membrane and a history of CSC than those without CVH. These findings may suggest that the pathologic mechanism common to CSC plays a role in the development of PCV lesion through some systemic or intraocular pathways.

Furthermore, PCV eyes with CVH were significantly related to persistent retinal fluid after 3 monthly intravitreal injections of ranibizumab. The relationship between CVH and poor responses to ranibizumab is uncertain. One possibility is that CVH might append additional exudation to the PCV lesion, which resulted in the persistent retinal fluid despite the repeated ranibizumab injections. Another possibility is that the pathologic background of PCV with CVH might have less of a relationship with VEGF than does PCV without CVH. In fact, VEGF concentrations in the aqueous humor have been shown to increase both in PCV and typical neovascular AMD, but VEGF levels in PCV were significantly lower than in typical neovascular AMD. Thus, there might be great variations in the contributions of VEGF among PCV cases.

Maruko and associates treated 16 PCV eyes using photodynamic therapy (PDT) with verteporfin. Curiously, all 10 eyes with CVH revealed decreased retinal thickness at 6 months after PDT, while 3 of 6 eyes without CVH showed increased retinal thickness. Although this study involved a small number of cases, the findings suggest CVH may be related to better treatment responses to PDT. By contrast, our results implicated that the presence of CVH seemed to be related to poor responses to intra-

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Figure 2. PCV with CVH. The right eye showed a characteristic orange-red lesion (yellow arrow) and exudative retinal detachment (A). FA demonstrated granular leakage of the dye in the macula (B). ICGA revealed a peculiar polypoidal structure (yellow arrow) and connecting branching choroidal vascular networks (white arrows) in the late phase. Note that multifocal CVH (arrows) was seen (C). At baseline, the vertical scan by EDI-OCT through the fovea revealed a thickened choroid of 350 μm (double-headed arrow) and an accumulation of subretinal fluid (D). One month after 3 monthly intravitreal injections of ranibizumab (E), there was still some residual subretinal fluid (arrow). Arrowheads in (D) and (E) indicate the inner surface of the sclera.
vitreal injections of ranibizumab. Although such discrepancy between 2 treatments needs further investigation, future treatment strategies for PCV may include the assessment of CVH or choroidal thickness.

**FUNDUS AUTOFLUORESCENCE FINDINGS IN PCV**

Another method we applied for further understanding of PCV in a separate study was FAF photography. We performed FAF photography on consecutive patients with PCV and typical neovascular occult AMD without classic CNV, using a fundus camera-based system.9

We found characteristic FAF findings in PCV (Figure 4). The sites of the PCV lesions showed 2 distinct FAF patterns: (1) confluent hypoautofluorescence at the polypoidal lesions (“punched-out lesion”); and (2) granular hypoautofluorescence at the branching choroidal vascular networks. The confluent hypoautofluorescence, most of which was surrounded by a hyperautofluorescent ring, was seen in 80.4% of PCV eyes but none of the typical neovascular AMD eyes. In addition, when compared with typical neovascular AMD cases, widespread RPE damage was more frequently observed in PCV cases, both in the affected eyes and in the unaffected fellow eyes. Based on these data, we speculate that subclinical stress induced by the hemodynamic changes in the choroid, probably CVH, might be put on the RPE layer, resulting in widespread hypoautofluorescence in eyes with PCV, and even in the contralateral eyes. Similar widespread RPE changes, shown by hypoautofluorescent findings, are also known to appear in CSC,19 and might suggest, at least in part, a common pathologic background between PCV and CSC.

**SUMMARY**

Relatively new imaging modalities, namely EDI-OCT and FAF photography, have been applied to gain new insights into the pathogenesis of PCV. EDI-OCT has revealed that PCV eyes have thicker choroid than typical neovascular AMD eyes. The cause of the thickened choroid in PCV could be attributed, at least in part, to CVH seen on ICGA. The presence of CVH was also related to bilateral occurrence of neovascular membrane, a history of CSC, and
poor responses to intravitreal injections of ranibizumab. Although PCV is considered to be a multifactorial disease, our results suggest that a pathogenic mechanism common to CSC might play a role in the development of the PCV lesion, and, in my opinion, future treatment strategies for PCV should consider the presence of CVH or the choroidal thickness. FAF imaging demonstrated the peculiar findings at the PCV lesion, especially “punched-out lesion” at the polyps, as well as widespread RPE damage both in the affected eyes and in the unaffected fellow eyes. Such FAF findings may prove valuable for supporting more definite diagnosis of PCV and imply that the development of PCV lesion may be partially related to the extensive choroidal circulatory disturbances similarly seen in CSC. It currently appears that ICGA is necessary for the accurate diagnosis of PCV. It is my hope, however, that noninvasive techniques, such as EDI-OCT and FAF photography, will replace invasive angiographic methods, allowing improved elucidation of the pathogenesis of PCV and more reasonable treatment strategies and management for patients.

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