Multimodal Imaging of Unaffected Fellow Eyes in Patients with Polypoidal Choroidal Vasculopathy and Neovascular Age-Related Macular Degeneration

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ABSTRACT

Objective: To identify retinal abnormalities in the unaffected fellow eyes of patients with unilateral polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (n-AMD).

Methods: In this cross-sectional, retrospective case series, the medical records of patients with PCV and n-AMD were reviewed and the baseline patient characteristics recorded. Abnormal findings on spectral-domain optical coherence tomography (SD-OCT) (steep/notched pigment epithelial detachment [PED], double-layer sign, hyporeflective lumen within the PED), fundus autofluorescence (FAF) (ring/patch patterns), and indocyanine green angiography (ICGA) (punctate hyperfluorescence spot [PHS]) were studied.

Results: Seventy-one fellow eyes of patients with PCV and 64 fellow eyes of patients with n-AMD were included. FAF showed abnormalities in 26 (36.6%) and 33 (51.6%) fellow eyes of those with PCV and n-AMD, respectively (p=0.081). SD-OCT detected abnormalities in 25 (35.2%) and 36 (56.3%) fellow eyes of those with PCV and n-AMD, respectively (p=0.014). ICGA detected PHS in 47 (66.2%) and 34 (53.1%) fellow eyes of PCV and n-AMD, respectively (p=0.122).

Conclusion: Multimodal imaging showed abnormalities in most asymptomatic fellow eyes of patients with PCV and n-AMD. Regular and long-term self-monitoring and fundus evaluation are important for these patients. The current findings support the differences in the pathogeneses of PCV and n-AMD.

Keywords: Multimodal imaging; fellow eye; Age-related macular degeneration; Polypoidal choroidal vasculopathy (Siriraj Med J 2021; 73: 121-127)

INTRODUCTION

Age-related macular degeneration (AMD) is a bilateral disease characterized by either bilateral drusen or retinal pigment epithelium (RPE) abnormalities. The deposition of lipid-rich material in the basal lamina of the RPE and the inner collagenous layer of Bruch's membrane has been reported in histologic studies of eyes with AMD and associated positively with choroidal neovascularization.[1,2] An estimated 20% of patients with AMD have neovascular AMD (n-AMD) and most have unilateral disease at presentation.[3] The fellow eyes of patients with n-AMD almost always have clinical abnormalities; however, the vision is unaffected.

Polypoidal choroidal vasculopathy (PCV) with a presentation of serosanguinous maculopathy is difficult to distinguish from n-AMD clinically, and many clinicians

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believe that PCV is a subtype of n-AMD. However, recent multimodal imaging studies have suggested different pathogeneses of PCV and AMD. PCV is a clinical manifestation within pachychoroid disease, which is a disease spectrum characterized by attenuation of the choriocapillaris overlaying dilated choroidal vessels and associated with pigmentation changes in RPE cells, RPE dysfunction, and new vessel formation.[4] Unlike AMD, the fundi of the fellow eyes of patients with PCV are usually unremarkable.

The fellow eyes of patients with unilateral n-AMD or PCV are the eyes that are at risk. Results from the Age Related Eye Disease Study showed that the highest risk level for progression to an advanced stage in the fellow eyes of patients with unilateral advanced AMD was 50% by 5 years and 71% by 10 years.[5,6] Imaging studies in those eyes may provide preclinical information about AMD and PCV and the difference in the disease pathogeneses. We used multimodal retinal imaging to identify the fundus abnormalities.

MATERIALS AND METHODS

The Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 057/2015) approved the study protocol. This study complied with the tenets of the Declaration of Helsinki (1964) and all of its subsequent provisions. This retrospective chart review was conducted in patients with PCV and n-AMD in the outpatient unit, Department of Ophthalmology, Siriraj Hospital, Mahidol University, between October 2012 and January 2016. All patients had been diagnosed with PCV or n-AMD based on fundus photography, spectral-domain optical coherence tomography (SD-OCT), fundus fluorescein angiography (FFA), and indocyanine green angiography (ICGA). We used the Everest study criteria to diagnose PCV based on clinical and ICGA findings[7]; to diagnose n-AMD, we adhered to the eligibility criteria given in the Macular Photocoagulation Study using FFA.[8]

The current study included only patients for whom data from SD-OCT, fundus autofluorescence (FAF), and ICGA from the fellow eyes were available. We excluded patients who underwent a previous macular laser treatment, photodynamic therapy, or intravitreous injections; patient with other macular diseases, such as macular scars, geographic atrophy, myopic maculopathy, and macular holes; and those with poor-quality images.

The data collection included the best-corrected visual acuity (BCVA), intraocular pressure, and any underlying systemic diseases. The fundus investigations included SD-OCT, FAF, and ICGA (Heidelberg Retina Angiography 2, Heidelberg Engineering, Inc., Heidelberg, Germany).

One co-author (S.P.) reviewed all the images included in the study. We set up a prototype image of each characteristic in each investigation as shown in Fig 1. The FAF findings were defined as abnormal hypo- or hyperautofluorescence, i.e., a ring pattern (round hypoautofluorescence surrounded by hyperautofluorescence ring), and a patch pattern (hypo/hyperautofluorescence patch without identification of round-shaped hypoautofluorescence)

The SD-OCT findings were categorized into four patterns[9,10]: 1) a steep pigment epithelium detachment (PED), defined as a steep, sharp, peak-like, perpendicular RPE elevation with underlying moderate reflectivity in the peak; 2) a notched PED, a PED with a V-shaped depression between two PEDs; 3) a double-layer sign; two highly reflective separated layers, defined as an undulating RPE line and the hyperreflective straight line of Bruch's membrane, and moderate hyperreflectivity between these two lines; and 4) a hyporeflective lumen within the PED, a delineated round/oval hyporeflective cavity in the PED.

The ICGA findings were punctate hyperfluorescence spots (PHS) in mid-phase (5 minutes) was the characteristic in ICGA.

Abnormal findings in all investigations were graded as present or absent. Statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Categorical data are presented as the number or number and percentage, and continuous data are presented as the mean ± standard deviation. The demographic data were summarized using descriptive statistics. The chi-square test was used to evaluate qualitative variables. $P< 0.05$ was considered statistically significant.

RESULTS

Two hundred and thirty-five eyes were enrolled in this study. We excluded 34 eyes with uncertain diagnoses, 35 with poor-quality retinal images, 30 with old fibrotic scars, and one previously treated eye. Ultimately, 71 unaffected fellow eyes of those with PCV (36.6% were right eyes) and 64 fellow eyes of those with n-AMD (46.9% were right eyes, p=0.23) were enrolled. The average patient ages were 64.8 years and 73.3 years for those with PCV and n-AMD, respectively (p<0.01). Thirty-eight patients (53.5%) in the PCV group and 25 (30%) of n-AMD group were women.

The mean logarithm of the minimum angle of resolution VA of the fellow eyes of those with PCV and n-AMD were, respectively, 0.23 and 0.36 (p=0.09). No significant differences among the groups were seen

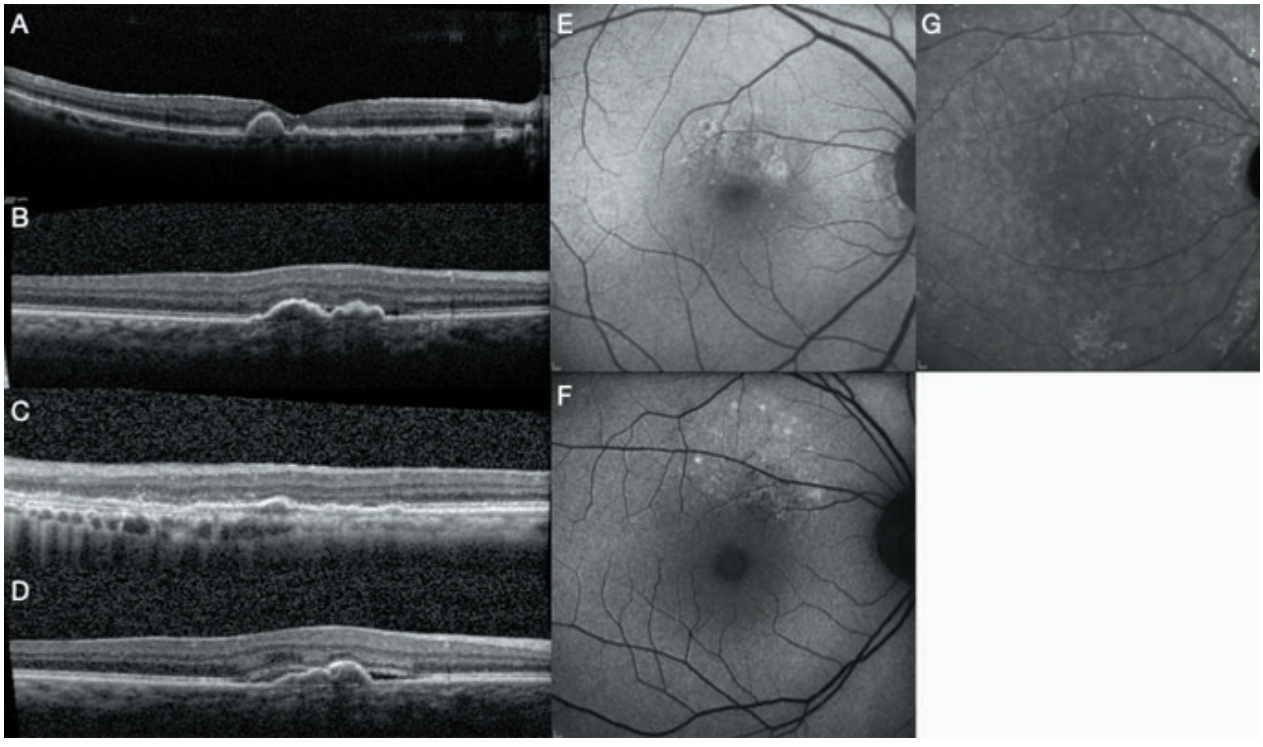

Fig 1. Representative images of abnormal imaging findings. Abnormal findings on spectral-domain optical coherence tomography (SD-OCT) images are classified as: **(A)** a steep pigment epithelial detachment (PED) characterized by steep/sharp peak-like and perpendicular elevation of the retinal pigment epithelium (RPE) with underlying moderate reflectivity in the peak; **(B)** a notched PED, a PED with a V-shaped depression between two PEDs; **(C)** a double-layer sign characterized by two highly reflective separated layers, which represent an undulating RPE line and a hyperreflective straight line of Bruch's membrane, and moderate hyperreflectivity between these two lines; and **(D)** a hyporeflective lumen in PED, which is a delineated round/oval sub-RPE cavity. Abnormal fundus autofluorescence is classified into two patterns: **(E)** a ring pattern, round hypoautofluorescence surrounded by a hyperautofluorescence ring and **(F)** a patch pattern, a hypo/hyperautofluorescence patch without identification of round-shaped hypoautofluorescence. **(G)** An abnormal finding in the indocyanine green angiography images is punctate hyperfluorescence spots characterized by multiple hyperfluorescent dots at the 5-minute time point.

in gender, laterality, or BCVA. However, patients with n-AMD were significantly older than those with PCV (Table 1).

Abnormalities of retinal imaging were found in 65 (91.5%) patients with PCV and 57 (89.1%) patients with AMD. Fundus autofluorescence showed abnormalities in 26 (36.6%) of those with PCV and in 33 (51.6%) of the fellow eyes of those with n-AMD (p=0.081). In the fellow eyes of those with PCV, a ring pattern was observed in eight eyes (11.3%) and a patch pattern in 18 eyes (25.4%). In the fellow eyes of those with n-AMD, ring and patch patterns were identified in 12 eyes (18.8%) and 21 eyes (32.8%), respectively.

SD-OCT detected abnormalities in 25 fellow eyes (35.2%) of those with PCV compared to 36 fellow eyes (56.3%) of those with n-AMD (p=0.014). In the PCV group, steep or notched PEDs were seen in 23.9%; whereas 1.4% and 11.3%, respectively, had a hyporeflective lumen or double-layer sign. In the n-AMD group, steep or notched PEDs and double-layer sign were found 46.9% and 10.9% respectively.

ICGA identified PHS in 47 (66.2%) fellow eyes of those with PCV and 34 (53.1%) fellow eyes of those with n-AMD (p=0.12) (Table 2). ICGA showed the highest rates of abnormalities compared to FAF and OCT in PCV (40.8%, 14.1% and 2.8%, respectively) and n-AMD (25%, 4.7%, and 7.8%, respectively).

Abnormalities in multimodality imaging were shown in Table 3. Only abnormal findings in both OCT and FAF were found significantly higher in n-AMD patients comparing with PCV patients, 23.4% and 8.5% respectively (p<0.01).

DISCUSSION

To the best of our knowledge, this is the first study to use multimodal imaging to evaluate the unaffected fellow eyes of patients with PCV and n-AMD. Based on previous reports, the rates of fellow eye involvement have

TABLE 1. Demographic data of the patients categorized by disease of affected eye.

	PCV	n-AMD	P-value
Number of eyes	71	64	
Gender n (%)			0.12
Male	33 (46.48)	39 (60.94)	
Female	38 (53.52)	25 (30.06)	
Age; min-max (mean)	2-82 (64.78)	56-90 (73.28)	<0.01
Laterality n (%)			0.23
Right	26 (36.62)	30 (46.88)	
Left	45 (63.38)	34 (53.12)	
BCVA; mean logMAR	0.23	0.36	0.09

Abbreviations: PCV, polypoidal choroidal vasculopathy; n-AMD, neovascular age related macular degeneration; BCVA, best corrected visual acuity; logMAR, logarithm of the Minimum Angle of Resolution.

TABLE 2. Abnormal findings in multimodal imaging.

	PCV n (%) Total 71 eyes	n-AMD n (%) Total 64 eyes	P-value
Abnormal findings in FAF	26 (36.6)	33 (51.6)	0.081
Ring pattern	8 (11.3)	12 (18.8)	
Patch pattern	18 (25.4)	21 (32.8)	
Abnormal findings in SD-OCT	25 (35.2)	36 (56.3)	0.014
Steep and/or notched PED	17 (23.9)	30 (46.9)	
Hyporeflective lumen within PED	1 (1.4)	0	
Double-layer sign	8 (11.3)	7 (10.9)	
Abnormal findings in ICGA			
Punctate hyperfluorescence spots	47 (66.2)	34 (53.1)	0.122

Abbreviations: PCV, polypoidal choroidal vasculopathy; n-AMD, neovascular age related macular degeneration; FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography; PED, pigment epithelium detachment; ICGA, indocyanine green angiography.

TABLE 3. Abnormal findings in combined modalities.

	PCV n (%) Total 71 eyes	n-AMD n (%) Total 64 eyes	P-value
SD-OCT and FAF	6 (8.5)	15 (23.4)	0.008
SD-OCT and ICGA	8 (11.3)	3 (4.7)	0.149
FAF and ICGA	1 (1.4)	2 (3.1)	0.501
SD-OCT, FAF and ICGA	9 (12.7)	13 (20.3)	0.232

Abbreviations: PCV, polypoidal choroidal vasculopathy; n-AMD, neovascular age related macular degeneration; FAF, fundus autofluorescence; SD-OCT, optical coherence tomography; ICGA, indocyanine green angiography.

ranged from about 6% to 11% in n-AMD and 12% in PCV.[11-15] This indicated that the unaffected fellow eyes of patients are the eyes at risk. Multimodal investigations are useful for early detection of diseases in asymptomatic fellow eyes and understanding disease pathogeneses.

Photoreceptor phagocytosis is a major function of RPE cells. When the RPE phagocytoses the photoreceptor outer segments, lipofuscin accumulates as an oxidative byproduct within the RPE cells. Lipofuscin contains the pigment A2E, which causes autofluorescence. Abnormalities of the RPE cells are accompanied by loss of A2E and lead to hypoautofluorescence.[16] In conditions in which the RPE has an incomplete phagocytosis process, excessive build-up of lipofuscin material and hyperautofluorescence in FAF can result.[10] Dysfunction of the RPE can present with either hypo or hyperautofluorescence depending on the disease stage. Therefore, FAF can indirectly represent the physiology of the RPE.

The pathogenesis of AMD begins with dysfunction in the RPE cells and leads to accumulation of both intracellular and extracellular material. Structural changes in the basement membrane of the RPE and lipid deposition in the inner aspect of Bruch's membrane have been reported in histologic studies of AMD.[1,2] Impaired permeability of nutrients and water in Bruch's membrane causes metabolic stress in the RPE cells and leads to consequent cellular atrophy or neovascular formation.[17] While the pathogenesis of PCV originates from the deep choroidal vessels, dilatation of the choroidal vessels in Haller's layer results in focal or diffuse attenuation of the inner choroidal vessel and choriocapillaris, which ultimately can affect the overlying RPE.[18-20] Therefore, in early-stage PCV, patients can present with unremarkable fundi if the RPE is not yet involved.

The current study showed FAF abnormalities in fewer fellow eyes of those with PCV than in the fellow eyes of those with n-AMD (36% vs. 51%, respectively). Moreover, the abnormalities seen on the SD-OCT images of the fellow eyes of those with PCV also were seen less often than in PVC (35% vs. 56%, respectively). Our explanation is that the pathogenesis of PCV originates in the choroid and FAF and SD-OCT can detect abnormalities only when the RPE is involved, not in the very early stage of PCV in which the RPE is still intact. While the pathogenesis of AMD begins in the RPE cells in which FAF can detect physiologic dysfunction and SD-OCT can visualize structural changes even in early stage, the current findings confirmed that the pathogeneses of AMD and PCV are distinct in origin. Furthermore, both FAF and SD-OCT can detect early abnormalities even in asymptomatic eyes.

SD-OCT can detect the structural changes in the RPE in many patterns and some of them are specific to PCV such as a steep PED, notched PED, double-layer sign, and hyporeflective lumen inside PEDs.[10] However, in the current study, all of the aforementioned patterns, except for the hyporeflective lumen inside the PEDs, also were detected in the fellow eyes of those with n-AMD. Therefore, a steep PED, notched PED, and double-layer sign may not be specific OCT findings of PCV.

In our study, fellow eyes with abnormalities in both OCT and FAF were found significantly higher in n-AMD which confirmed the pathogenesis of AMD originates from RPE dysfunction as mentioned earlier. While other combinations of imaging did not show significant correlation with PCV or n-AMD. Yamagishi and colleagues[23] described abnormal FAF in PCV as confluent hypoautofluorescence represented by well-

demarcated hypoautofluorescence surrounded by hyperautofluorescence, which we refer to as the ring pattern in the current study. This finding was associated with the polypoidal lesions seen on ICGA images. This characteristic was observed in most eyes with PCV and not in typical n-AMD. Those authors proposed that the anterior protrusion of polyp lesions may induce RPE damage.[21] However, in the current study, a ring pattern also was seen in 18% of the fellow eyes of those with n-AMD. Therefore, this finding in FAF may not be specific to PCV. Any pathology that involves the RPE and causes RPE damage can demonstrate a ring pattern as well, while a patch pattern, represented by hypo/hyperautofluorescence, is a nonspecific FAF finding that may represent changes in RPE function in early-stage diseases of the RPE cells and adjacent structures.

ICGA is an invasive investigation. Because of its longer operating wavelength, ICG can fluorescence through the RPE better than fluorescein dye. ICGA is useful for detecting abnormal choroidal vasculature. The specific characteristics of ICGA in PCV were reported and used as diagnostic criteria.[7] However, a non-specific finding in ICGA, such as PHS, has been described previously in choroidal vasculopathy disorders. Those punctate spots were believed to be in the inner choroid and possibly the RPE layer and were found to be associated with the hyperpermeability of the choroidal vessels causing dye leakage in the late phase.[22,23] Park and colleagues[26] reported a higher incidence of PHS in PCV than n-AMD in affected and contralateral eyes. Those authors suggested that PCV may arise from choroidopathy and be distinct from typical n-AMD.[24] In the current study, PHS was detected in the fellow eyes of those with PCV and n-AMD and the difference did not reach significance (66% in PCV vs. 53% in n-AMD). Because the punctate spots can be present in either the inner choroid or RPE, this nonspecific finding may be associated with both PCV and AMD. Therefore, PHS may not be a finding specific to PCV, in that it can be detected in AMD as well.

In the current study, compared to FAF and SD-OCT, ICGA detected the most abnormalities in the fellow eyes of those with PCV. About two-thirds of the fellow eyes of those with PCV had abnormalities on ICGA images compared with only one-third of patients with abnormalities on FAF or SD-OCT images. This result may suggest that patients who have normal findings on FAF or SD-OCT still have a risk of developing PCV in their fellow eyes and those eyes should be monitored regularly. Although ICGA seems to be the best investigation for detecting choroidal pathologies, especially in early or even preclinical disease stages, ICGA is not likely to be performed during routine screenings because it is invasive and complex. FAF and SD-OCT are noninvasive and reproducible investigations, so they are more likely to be used for screening PCV in asymptomatic eyes, even though their abilities to detect abnormalities are lower than that of ICGA.

The current study had several limitations. The retrospective cross-sectional design may cause a systematic bias toward population selection. The small sample size and lack of follow-up also were drawbacks. Finally, the evaluation of all images was lacking in quantitative analysis results in subjective information.

In conclusion, most asymptomatic fellow eyes of those with PCV and n-AMD, which are the better eyes of patients, showed abnormalities in all current investigations and may represent the eyes at risk. Patients and physicians should be more concerned about the status of these eyes. The correlation between abnormal findings in each imaging modality may contribute to important information that can predict possible disease progression. Additional longitudinal long-term studies may facilitate a better understanding of the pathogeneses and course of these diseases.

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