Choroidal Thickness, Vascular Hyperpermeability, and Complement Factor H in Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy

Pichai Jirarattanasopa,[1,2] *Sotaro Ooto,*[1] *Isao Nakata,*[1] *Akitaka Tsujikawa,*[1] *Kenji Yamashiro,*[1] *Akio Oishi,*[1] *and Nagahisa Yoshimura*[1]

Purpose. To investigate the relationship between subfoveal choroidal thickness, choroidal vascular hyperpermeability, and complement factor H (*CFH*) gene polymorphism in typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

Methods. Fifty-eight patients with typical AMD and 63 patients with PCV underwent fluorescein angiography, indocyanine green angiography (IA), and spectral-domain optical coherence tomography (OCT) using enhanced depth imaging (EDI). Subfoveal choroidal thickness was measured using EDI-OCT images, and choroidal hyperpermeability was evaluated using late-phase IA images. The major AMD-associated single-nucleotide polymorphisms were genotyped in 86 patients.

Results. Mean subfoveal choroidal thickness was significantly lower in eyes with typical AMD than that in eyes with PCV ($P = 0.025$). Subfoveal choroidal thickness was greater in eyes with choroidal hyperpermeability than that in eyes without it in typical AMD ($P < 0.001$) and PCV ($P = 0.020$), and in the fellow eyes of typical AMD ($P < 0.001$) and PCV ($P = 0.027$). In eyes without choroidal hyperpermeability, the mean subfoveal choroidal thickness was greater in PCV than that in typical AMD ($P = 0.001$). Choroidal thickness decreased after photodynamic therapy combined with intravitreal ranibizumab in typical AMD ($P = 0.016$) and PCV ($P = 0.036$). In eyes with PCV, the I62V polymorphism in the *CFH* gene contributed to choroidal thickness ($P = 0.043$).

Conclusions. Choroidal thickness is related to the AMD subtypes, choroidal hyperpermeability, and I62V *CFH* gene polymorphism. In eyes without choroidal hyperpermeability, EDI-OCT is useful as an auxiliary measure for differentiating typical AMD and PCV. (*Invest Ophthalmol Vis Sci.* 2012; 53:3663–3672) DOI:10.1167/iovs.12-9619

Exudative age-related macular degeneration (AMD) is the leading cause of severe impairment of visual function in people older than 50 years of age who reside in industrialized countries. Maruko et al.[1] surveyed the distribution of exudative AMD subtypes in a Japanese population and showed that 35% of patients had typical AMD and 55% had polypoidal choroidal vasculopathy (PCV), which is characterized by orange subretinal polypoidal dilations arising from the choroidal vascular network.[2] Although verteporfin photodynamic therapy (PDT) tends to be of benefit in PCV,[3] antivascular endothelial growth factor (VEGF) therapy does not appear to diminish the polypoidal lesions.[4–6] In contrast, in eyes with typical AMD, anti-VEGF therapy provides greater clinical benefit than PDT.[7]

Indocyanine angiography (IA) has improved our knowledge of many macular diseases including typical AMD and PCV.[8–14] Choroidal vascular hyperpermeability is frequently seen in eyes with central serous chorioretinopathy,[8–11,14] but it is also seen in PCV and typical AMD,[13] suggesting that choroidal vascular abnormalities may be involved in the pathogenesis of these diseases. Since Spaide and colleagues[15] introduced enhanced depth imaging optical coherence tomography (EDI-OCT), an increasing number of investigators have studied choroidal thickness in healthy and diseased eyes.[16–26] Recently, several researchers have reported that subfoveal choroidal thickness is greater in eyes with PCV than that in eyes with typical AMD,[22–24] suggesting the involvement of different pathogenic mechanisms in typical AMD and PCV. However, little is known about the relationship between choroidal thickness, angiographic changes, and genetic background in these eyes.

In this study, we investigated a consecutive series of treatment-naïve patients with typical AMD and PCV to evaluate the relationship between the choroidal thickness on EDI-OCT, choroidal vascular hyperpermeability on IA, and major AMD-associated single nucleotide polymorphisms (SNPs; polymorphisms in the complement factor H [*CFH*] and age-related maculopathy susceptibility 2 [*ARMS2*] genes) in these two disorders.

Methods

All investigations adhered to the tenets of the Declaration of Helsinki, and the study was approved by the institutional review board and the ethics committee at Kyoto University Graduate School of Medicine. The nature of the study and its possible consequences were explained to the study candidates, after which written informed consent was obtained from all patients who were genotyped.

Subjects

We retrospectively reviewed medical charts of 121 consecutive treatment-naïve patients (58 patients with typical AMD and 63 patients with PCV) who visited the Macular Service at Kyoto University Hospital, Kyoto, Japan, between April 2009 and October 2011. All patients with typical AMD and PCV underwent best-corrected visual acuity (BCVA),

From the [1]Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan; and the [2]Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.

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Corresponding author: Sotaro Ooto, Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan; ohoto@kuhp.kyoto-u.ac.jp.

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intraocular pressure, autorefractometry/keratometry, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, color fundus photography, fluorescein angiography (FA), IA using a confocal laser scanning ophthalmoscope (HRA2; Heidelberg Engineering GmbH, Dossenheim, Germany), and spectral-domain (SD)-OCT (Spectralis; Heidelberg Engineering) using an EDI technique at baseline.

Diagnoses of typical AMD and PCV were based on the results of fundus examination, FA, IA, and OCT. Typical AMD was diagnosed in patients older than 50 years of age, with evidence of hyperfluorescence with late leakage on FA associated with pigment epithelium detachment (PED), serous retinal detachment (SRD), subretinal exudation, and hemorrhage in the macular region. PCV was diagnosed primarily on the basis of IA findings, branching vascular network, and terminating polypoidal lesions. All diagnoses were made by three retinal specialists (SO, KY, and AT); a fourth specialist (NY) was called on when the diagnosis could not be decided on by the initial three reviewers.

Exclusion criteria included the presence of high myopia with refractive error ≥ -6.0 diopters or axial length ≥ 26.5 mm; history of intraocular surgery including vitrectomy, cataract surgery (within 1 year before the measurement), anti-VEGF therapy, and PDT; history of ocular trauma; evidence of other retinal diseases including other neovascular maculopathy (i.e., retinal angiomatous proliferation, angioid streaks, idiopathic macular telangiectasia), glaucoma or high intraocular pressure ($\geq$22 mm Hg); and poor image due to media opacity, thick subretinal hemorrhage, or unstable fixation. Subjects with systemic diseases or conditions such as diabetes mellitus or malignant hypertension that might affect choroidal thickness were also excluded.

Choroidal Hyperpermeability

Choroidal vascular hyperpermeability was evaluated in the late phase of IA, approximately 10–15 minutes after dye injection. According to the report by Guyer et al.,[8] choroidal vascular hyperpermeability was defined as multifocal areas of hyperfluorescence with blurred margins within the choroid (Fig. 1). Choroidal vascular hyperpermeability was evaluated in the late phase of IA by an experienced ophthalmologist (SO) who was masked to the EDI-OCT images. In the present study, all eyes with choroidal vascular hyperpermeability showed minimal extension of the focal hyperfluorescent area.

OCT System and Thickness Measurement

Choroidal thickness was measured using the EDI technique,[15] which was performed by placing the SD-OCT (Spectralis; Heidelberg Engineering) instrument close enough to the eye to obtain an inverted image. All images were obtained using an eye-tracking system, and 100 scans were averaged automatically to improve the signal-to-noise ratio. The subfoveal choroidal thickness, defined as the vertical distance between the hyperreflective line of Bruch's membrane and the chorioscleral interface, was measured using the horizontal and vertical line scans through the center of the fovea. All measurements were performed manually using a built-in caliber by a trained ophthalmologist (PJ) blinded to the study parameters including diagnosis, angiographic findings, and genotype. Each thickness was determined as the mean thickness using vertical and horizontal B-scan images through the center of the fovea.

In B-scans where it was difficult to identify the entire outer choroid, 5–10 points at which the chorioscleral interface could be identified were chosen and connected to create a segmentation line. The subfoveal choroidal thickness was measured after the segmentation lines were created. If the thickness differed remarkably between the horizontal and vertical B-scans, the segmentation lines of the B-scans were rechecked and corrected as required.

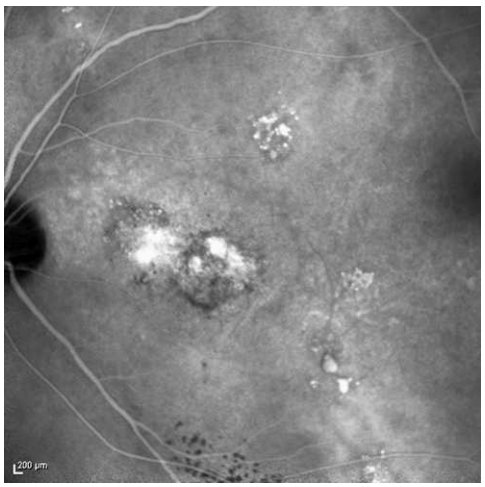

Figure 1. Choroidal vascular hyperpermeability. Choroidal vascular hyperpermeability was evaluated in the late phase of indocyanine green angiography (IA), 10–15 minutes after injection of dye. Choroidal hyperpermeability is seen as multifocal areas of hyperfluorescence with blurred margins.

Treatments

Patients who had a visual disturbance due to typical AMD and PCV were offered anti-VEGF therapy or PDT combined with anti-VEGF therapy. All eyes treated by intravitreous ranibizumab monotherapy ($n = 63$; 31 eyes with typical AMD and 32 eyes with PCV) received three successive intravitreal injections of ranibizumab at monthly intervals. Injections of ranibizumab were performed under sterile conditions, and prophylactic topical antibiotics were applied for 1 week after the injection.

In all eyes treated by PDT combined with intravitreal ranibizumab ($n = 16$; 10 eyes with typical AMD and 6 eyes with PCV), ranibizumab injections were performed in a sterile manner and prophylactic topical antibiotics were applied for 1 week after the injection. At 3–4 days after the intravitreal injection of ranibizumab, normal-fluence PDT was performed using a 689-nm diode laser unit (Visulas PDT system 690S; Carl Zeiss Meditec, Dublin, CA) after an injection of verteporfin, according to PDT guidelines for AMD. The greatest linear dimension chosen was based on fluorescein and indocyanine green angiograms. All polypoidal lesions, the entire vascular network, and choroidal neovascularization (CNV) detected with fluorescein or indocyanine green angiography were included.

Genotyping

Genomic DNA was prepared from peripheral blood leukocytes of 86 patients (41 patients with typical AMD and 45 patients with PCV) with a DNA extraction kit (QuickGene-610L; Fujifilm, Tokyo, Japan). We genotyped the major AMD-associated SNPs, *CFH* Y402 rs1061170, *CFH* I62V rs800292, and *ARMS2* A69S rs10490924, using SNP genotyping assays (*Taq*Man SNP Assay, ABI PRISM 7700 system; Applied Biosystems, Inc., Foster City, CA) according to the manufacturer's instructions. To evaluate the association of choroidal thickness or choroidal hyperpermeability and genotyping, data from the right eye were selected in patients with bilateral diseases.

Statistical Analyses

An independent sample *t*-test was used to compare variables between typical AMD eyes and PCV eyes, and between eyes with unilateral disease and unaffected fellow eyes. The paired-sample *t*-test was used to compare mean choroidal thickness before and after treatment. To evaluate the genotype effect, an allelic χ^2 test 2×2 table was used. To evaluate choroidal thickness trends according to each genotype, the Jonckheere–Terpstra test was used. All statistical evaluations were performed using commercially available software (SPSS20; IBM, Armonk, NY). Values of $P < 0.05$ were considered to indicate statistical significance.

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Table 1. Demographic Data and Subfoveal Choroidal Thickness in Typical AMD and PCV

	Typical AMD	PCV	*P* Value (*t*-test)
n	64	65	
Age (y)	76.3 ± 8.1	73.3 ± 8.0	0.037
Refractive error (diopter)	0.6 ± 2.0	0.1 ± 1.8	0.152
Subfoveal CT (μm)	203.6 ± 105.9	243.3 ± 92.9	0.025

CT, choroidal thickness.

Results

In the present study, 64 eyes of 58 patients and 65 eyes of 63 patients were diagnosed as typical AMD and PCV, respectively. Mean age was 76.3 ± 8.1 years in patients with AMD and 73.3 ± 8.0 years in patients with PCV ($P = 0.037$, *t*-test). The mean refractive error was 0.6 ± 2.0 diopters in eyes with typical AMD and 0.1 ± 1.8 diopters in eyes with PCV ($P = 0.152$, *t*-test) (Table 1).

Choroidal Thickness in Typical AMD and PCV

The mean subfoveal choroidal thickness was significantly thinner in eyes with typical AMD (203.6 ± 105.9 μm) than that in eyes with PCV (243.4 ± 92.9 μm, $P = 0.025$, *t*-test) (Table 1). In patients older than 70 years of age, subfoveal choroidal thickness was significantly thinner in eyes with typical AMD (169.6 ± 89.4 μm) than that in eyes with PCV (236.3 ± 87.0 μm, $P < 0.001$, *t*-test). In typical AMD, the mean subfoveal choroidal thickness in eyes with choroidal vascular hyperpermeability on IA was significantly greater than that in eyes without it ($P < 0.001$, *t*-test) (Figs. 2 and 3, Table 2).

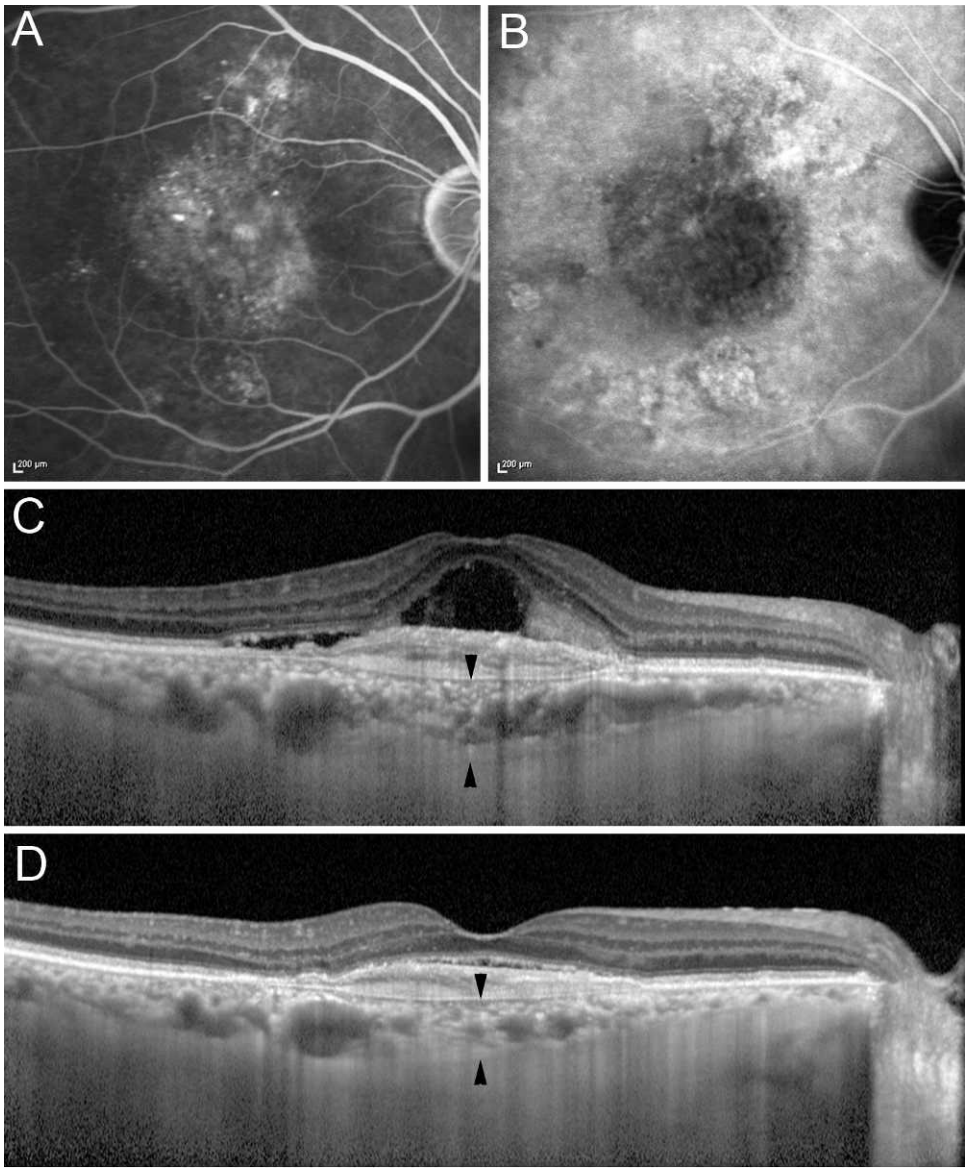

Figure 2. Typical AMD with choroidal hyperpermeability. (**A**) FA shows late leakage. (**B**) Late-phase IA shows choroidal vascular hyperpermeability. (**C**) EDI-OCT shows SRD, subretinal exudation, fibrovascular PED, and thick choroid. Subfoveal choroidal thickness was 320 μm (*between arrowheads*). (**D**) At 3 months after photodynamic therapy combined with intravitreal ranibizumab, EDI-OCT shows almost resolved SRD and decreased choroidal thickness. Subfoveal choroidal thickness was 258 μm (*between arrowheads*).

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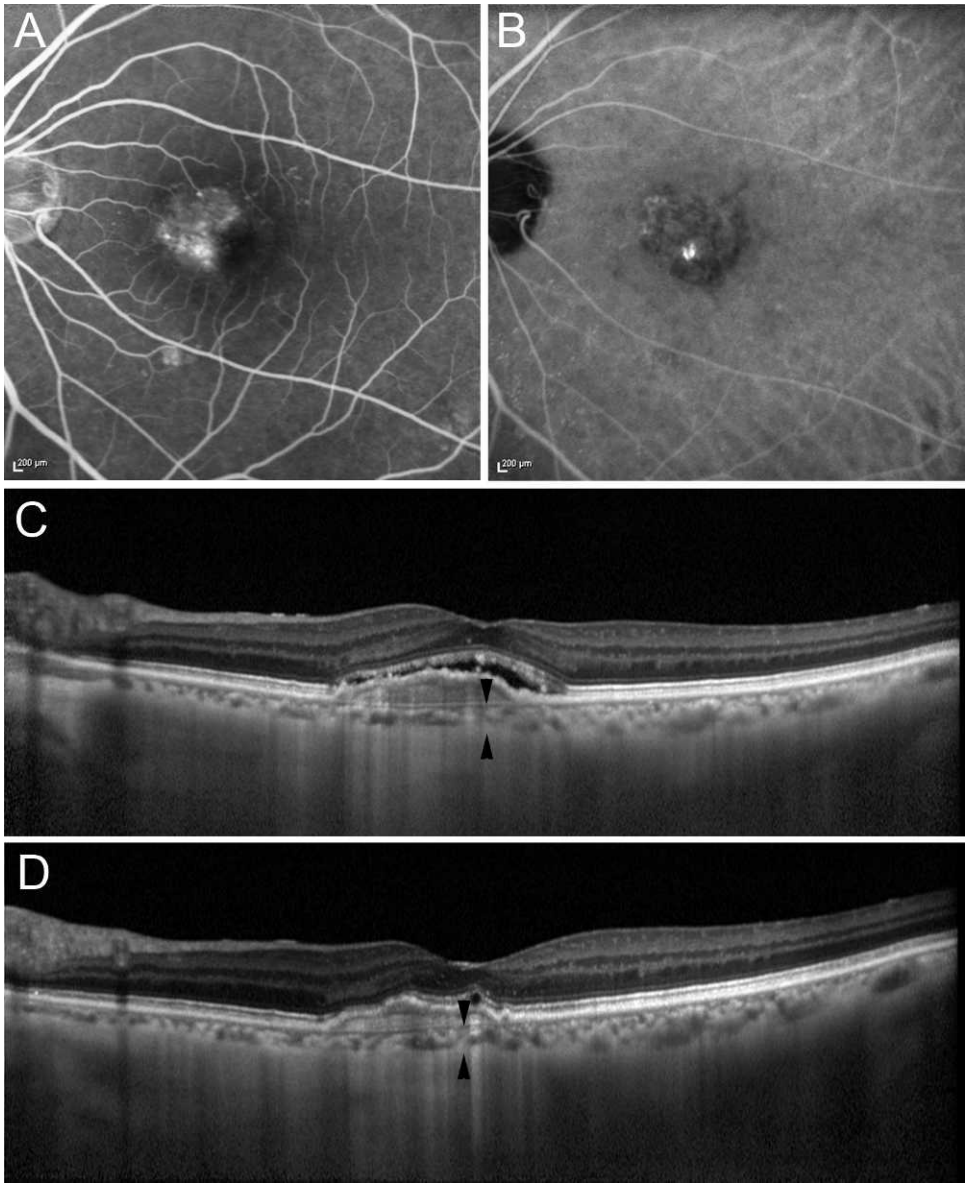

Figure 3. Typical AMD without choroidal hyperpermeability. (**A**) FA shows late leakage. (**B**) Late-phase IA shows no choroidal hyperpermeability. (**C**) EDI-OCT shows SRD, fibrovascular PED, and thin choroid. Subfoveal choroidal thickness was 134 μm (*between arrowheads*). (**D**) After 3 monthly injections of intravitreal ranibizumab, EDI-OCT shows resolution of SRD and stable choroidal thickness. Subfoveal choroidal thickness was 134 μm (*between arrowheads*).

Similarly in PCV, the mean subfoveal choroidal thickness in eyes with choroidal vascular hyperpermeability on IA was significantly greater than that in eyes without it ($P = 0.020$, *t*-test) (Figs. 4 and 5, Table 2).

In eyes with choroidal hyperpermeability, mean subfoveal choroidal thickness was similar between eyes with typical AMD and PCV ($P = 0.848$, *t*-test) (Table 2). In contrast, in eyes without choroidal vascular hyperpermeability, the mean

Table 2. Subfoveal Choroidal Thickness and Choroidal Hyperpermeability

		With Choroidal Hyperpermeability	Without Choroidal Hyperpermeability	*P* Value (*t*-test)
Typical AMD ($n = 64$)	*n*	24	40	
	Subfoveal CT (μm)	278.2 ± 98.7 (μm)	158.9 ± 83.1 (μm)	<0.001
PCV ($n = 65$)	*n*	20	45	
	Subfoveal CT (μm)	283.4 ± 77.4 (μm)	225.7 ± 94.5 (μm)	0.020
P value (*t*-test)		0.848	0.001	

CT, choroidal thickness.

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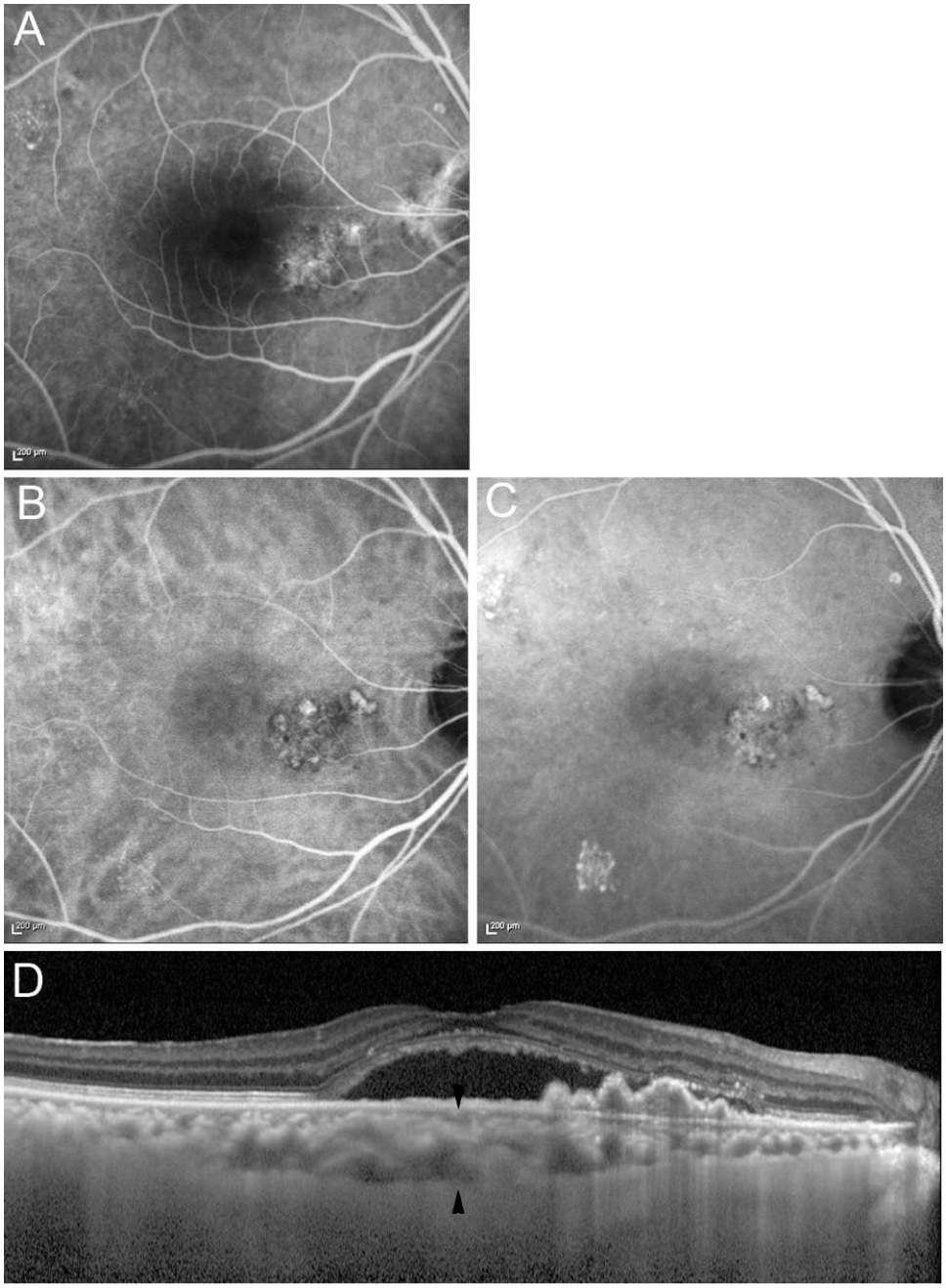

Figure 4. PCV with choroidal hyperpermeability. (**A**) FA shows late leakage. (**B**) Middle-phase IA shows a branching vascular network that terminates in polypoid lesions. (**C**) Late-phase IA shows choroidal vascular hyperpermeability. (**D**) EDI-OCT shows SRD, protrusions of the RPE suggesting polypoidal lesions, and thick choroid. Subfoveal choroidal thickness was 310 μm (*between arrowheads*).

subfoveal choroidal thickness was significantly greater in eyes with PCV than that in eyes with typical AMD ($P = 0.001$, *t*-test) (Figs. 3 and 5, Table 2).

Choroidal Thickness in Unilateral Disease Eyes and Fellow Eyes

In the present study, EDI-OCT had been performed in both eyes in 101 patients with unilateral diseases; thus, subfoveal choroidal thickness in unilateral disease eyes and fellow eyes was compared in these patients. In patients with unilateral typical AMD and PCV, no significant difference was observed between the mean subfoveal choroidal thickness in disease eyes and fellow eyes ($P = 0.938$ in typical AMD and $P = 0.996$ in PCV, *t*-test) (Table 3). Mean subfoveal choroidal thickness was significantly thinner in eyes with typical AMD than that in eyes with PCV both in disease eyes ($P = 0.023$, *t*-test) and in fellow eyes ($P = 0.026$, *t*-test) (Table 3). In the fellow eyes of patients with typical AMD, the mean subfoveal choroidal thickness was significantly greater in eyes with choroidal vascular hyperpermeability on IA than that in eyes without it ($P < 0.001$, *t*-test) (Table 4). Similarly, in the fellow eyes of patients with PCV, the mean subfoveal choroidal thickness was significantly greater in eyes with choroidal vascular hyperpermeability on IA than that in eyes without it ($P = 0.027$, *t*-test) (Table 4).

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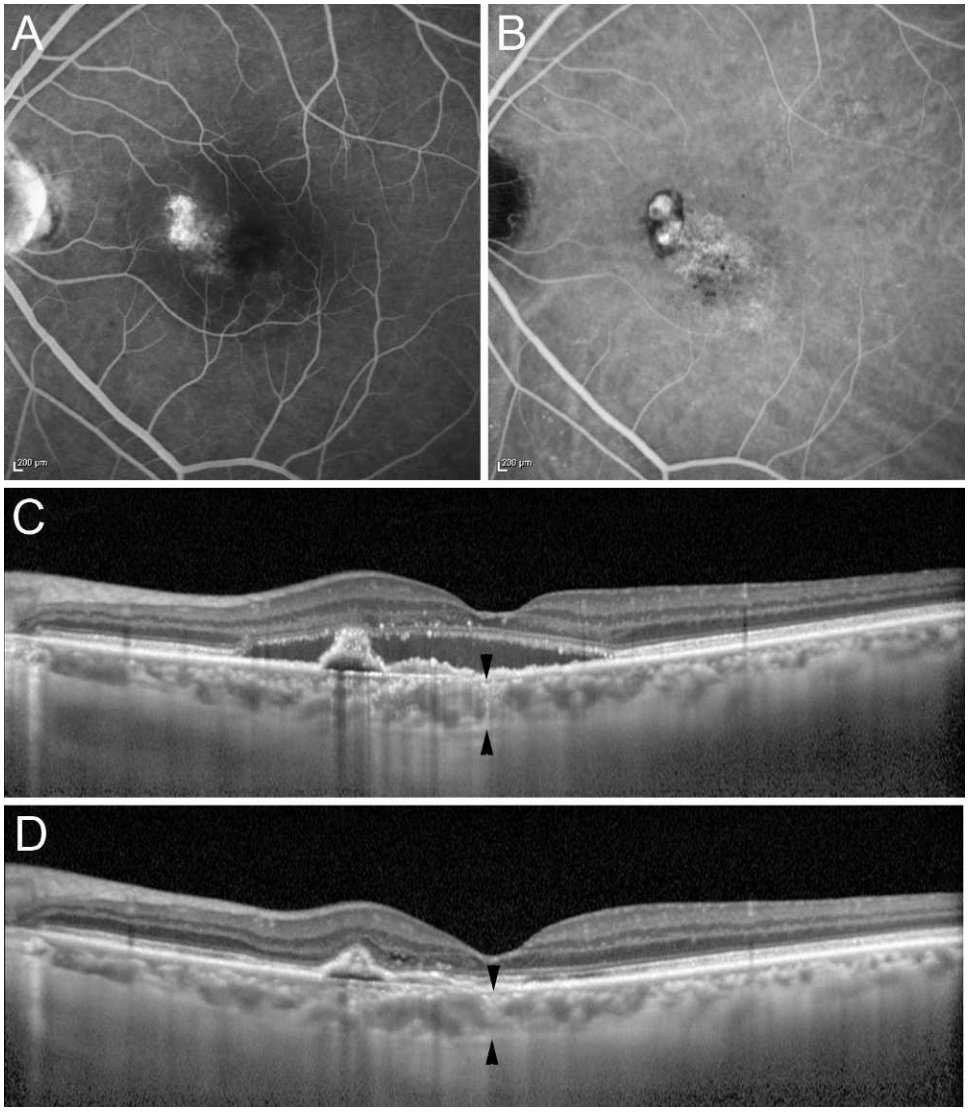

Figure 5. PCV without choroidal hyperpermeability. (**A**) FA shows late leakage. (**B**) Late-phase IA shows a branching vascular network that terminates in polypoid lesions, but shows no choroidal hyperpermeability. (**C**) EDI-OCT shows SRD, protrusions of the RPE, and thinner choroid compared with Figure 4. Subfoveal choroidal thickness was 230 μm (*between arrowheads*). (**D**) After 3 monthly injections of intravitreal ranibizumab, EDI-OCT shows resolution of SRD and almost stable choroidal thickness. Subfoveal choroidal thickness was 222 μm (*between arrowheads*).

In eyes with choroidal hyperpermeability, mean subfoveal choroidal thickness was not different between the fellow eyes of patients with typical AMD and PCV ($P = 0.401$, *t*-test) (Table 4). In contrast, in eyes without choroidal vascular hyperpermeability, the mean subfoveal choroidal thickness was significantly greater in the fellow eyes of patients with PCV than that in the fellow eyes of patients with typical AMD ($P = 0.004$, *t*-test) (Table 4).

Table 3. Subfoveal Choroidal Thickness in Unilateral Disease Eyes and Fellow Eyes

	Disease Eyes	Fellow Eyes	*P* Value (*t*-test)
Typical AMD ($n = 47$)	202.1 ± 88.4 (μm)	203.5 ± 83.6 (μm)	0.938
PCV ($n = 54$)	242.3 ± 86.6 (μm)	242.4 ± 88.5 (μm)	0.996
P value (*t*-test)	0.023	0.026	

With bilateral choroidal hyperpermeability, mean subfoveal choroidal thickness was similar in eyes with typical AMD/PCV and fellow eyes (Table 5).

Choroidal Thickness Changes after Treatment

After combination therapy (PDT and intravitreous ranibizumab), the mean subfoveal choroidal thickness was decreased in typical AMD and PCV ($P = 0.054$ in eyes with choroidal hyperpermeability and $P = 0.010$ in eyes without choroidal hyperpermeability, paired *t*-test) (Table 6). In eyes with typical AMD, subfoveal choroidal thickness decreased from 234.7 ± 114.2 to 191.4 ± 111.2 μm 3 months after PDT combined with intravitreal ranibizumab ($P = 0.016$, paired *t*-test) (Fig. 2). In eyes with PCV, subfoveal choroidal thickness decreased from 201.0 ± 101.1 to 172.9 ± 91.0 μm 3 months after PDT combined with intravitreal ranibizumab ($P = 0.036$, paired *t*-test). In contrast, three injections of intravitreous ranibizumab did not decrease subfoveal choroidal thickness in typical AMD

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Table 4. Subfoveal Choroidal Thickness and Choroidal Hyperpermeability in Fellow Eyes

		With Choroidal Hyperpermeability	Without Choroidal Hyperpermeability	*P* Value (*t*-test)
Fellow eyes of typical AMD ($n = 47$)	*n*	19	28	
	Subfoveal CT (μm)	258.6 ± 69.8 (μm)	166.1 ± 71.1 (μm)	<0.001
Fellow eyes of PCV ($n = 54$)	*n*	17	37	
	Subfoveal CT (μm)	280.4 ± 83.8 (μm)	224.8 ± 83.5 (μm)	0.027
P value (*t*-test)		0.401	0.004	

CT, choroidal thickness.

and PCV ($P = 0.415$ in eyes with choroidal hyperpermeability and $P = 0.173$ in eyes without choroidal hyperpermeability, paired *t*-test) (Table 6, Figs. 3 and 5).

Visual acuity improved after monthly injections of intravitreal ranibizumab regardless of choroidal hyperpermeability (Table 7). In contrast, visual acuity was stable after PDT combined with intravitreal ranibizumab regardless of choroidal hyperpermeability (Table 7).

Genomic Association

The I62V polymorphism in the *CFH* gene seemed to contribute to choroidal thickness. Mean subfoveal choroidal thickness was 247.5 ± 97.7 μm in genotype AA, 248.2 ± 97.6 μm in genotype GA, and 221.9 ± 102.7 μm in genotype GG ($P = 0.117$, Jonckheere–Terpstra test) (Fig. 6). Specifically in eyes with PCV, mean subfoveal choroidal thickness was 274.9 ± 79.0 μm in genotype AA, 273.9 ± 99.2 μm in genotype GA, and 219.5 ± 90.0 μm in genotype GG ($P = 0.043$, Jonckheere–Terpstra test) (Fig. 6). In contrast, the Y402H polymorphism in the *CFH* gene and the A69S polymorphism in the *ARMS2* gene did not contribute to subfoveal choroidal thickness ($P = 0.461$ and 0.248, respectively, Jonckheere–Terpstra test).

The frequency of the minor allele in *CFH* I62V polymorphism was 34% in patients with choroidal hyperpermeability and 24% in patients without choroidal hyperpermeability (Table 8). Upon analyzing the genotypes using the 2 × 2 table from the allelic χ^2 test, the G allele did not contribute to choroidal hyperpermeability ($P = 0.169$). The T allele and C allele in *CFH* Y402H and *ARMS2* A69S, respectively, also did not contribute to choroidal hyperpermeability ($P = 0.575$ and 0.244, respectively).

Discussion

Several researchers have reported on the subfoveal choroidal thickness in eyes with PCV and typical AMD.[21–24] However, little is known about the relationship between choroidal thickness and angiographic changes or genotypes in these eyes. In the present study, we investigated a consecutive series of treatment-naïve patients with typical AMD and PCV and found a relationship between choroidal thickness and subtypes of AMD, choroidal vascular hyperpermeability, and polymorphisms in the *CFH* gene in these diseases.

Table 5. Subfoveal Choroidal Thickness in Disease Eyes and Fellow Eyes with Bilateral Choroidal Hyperpermeability

	Disease Eyes	Fellow Eyes	*P* Value (*t*-test)
Typical AMD ($n = 7$)	251.6 ± 87.9	258.3 ± 80.7	0.885
PCV ($n = 11$)	274.8 ± 96.2	255.2 ± 77.5	0.606
P value (*t*-test)	0.615	0.937	

Subfoveal choroidal thickness was reported to be greater in eyes with PCV than that in eyes with typical AMD,[22–24] which is consistent with the present study. In addition, in the present study, subfoveal choroidal thickness of the fellow eyes was greater in eyes with PCV than that in eyes with typical AMD. These differences in choroidal thickness may indicate a significant structural difference in the choroid between typical AMD and PCV.

In eyes without choroidal vascular hyperpermeability, the mean subfoveal choroidal thickness was significantly greater in eyes with PCV than that in eyes with typical AMD. The same was true in the fellow eyes of patients with typical AMD and PCV. Thus, in eyes without choroidal hyperpermeability, the difference in choroidal thickness may reflect the different pathologic mechanisms of the two diseases. The decreased ability of the choroid to deliver oxygen and other metabolites to the retina, which is due mainly to choroidal blood volume rather than velocity of flow, has been postulated to lead to CNV in typical AMD.[27] Our results showing thinner choroidal thickness in eyes with typical AMD may be explained by this postulation. In addition, dilation of choroidal vessels and a collection of dilated thin-walled vessels derived from choroidal vessels beneath the retinal pigment epithelium (RPE) have been noted in histopathologic studies of PCV.[28–31] The present results regarding choroidal thickness of PCV may reflect those of histologic studies.

Choroidal thickness has a relationship not only with subtypes of AMD but also with choroidal vascular hyperpermeability. Maruko et al.[21] reported that choroid in PCV eyes with choroidal hyperpermeability was thicker than that in eyes without choroidal hyperpermeability, consistent with the present study. We first showed that, in typical AMD, the mean subfoveal choroidal thickness in eyes with choroidal vascular hyperpermeability on IA was significantly greater than that in eyes without it. In addition, in the fellow eyes of patients with typical AMD and PCV, the mean subfoveal choroidal thickness in eyes with choroidal vascular hyperpermeability on IA was significantly greater than that in eyes without it. These findings suggest that choroidal thickening is closely associated with choroidal hyperpermeability both in typical AMD and PCV, and both in disease eyes and fellow eyes. Thus, typical AMD and PCV may share, at least in part, a common pathology with choroidal vascular abnormalities with regard to choroidal hyperpermeability. In fact, in eyes with choroidal hyperpermeability, the mean choroidal thickness was similar between eyes with typical AMD and PCV. Hydrostatic pressure within the choroid may increase in areas with choroidal vascular hyperpermeability, resulting in increased extravascular volume within the choroid and increased choroidal thickness in typical AMD and PCV with choroidal hyperpermeability.

Recently, Maruko et al.[21] reported that subfoveal choroidal thickness was decreased by PDT monotherapy and PDT combined with intravitreous ranibizumab in eyes with PCV. In the present study, after PDT combined with intravitreous

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Table 6. Mean Subfoveal Choroidal Thickness Change before and after Treatment in Eyes with and without Choroidal Vascular Hyperpermeability

	Treatment (*n*)	Baseline	3-Month Follow-up	*P* Value (*t*-test)
With choroidal hyperpermeability	PDT + IVR (6)	292.8 ± 89.2	240.1 ± 103.4	0.054
	Mono-IVR (20)	286.1 ± 105.5	288.1 ± 106.2	0.415
Without choroidal hyperpermeability	PDT + IVR (10)	170.3 ± 97.4	133.1 ± 82.4	0.010
	Mono-IVR (43)	200.8 ± 106.4	198.0 ± 109.0	0.173

Treatment consisted of intravitreal ranibizumab monotherapy or PDT combined with intravitreal ranibizumab. IVR, intravitreal ranibizumab.

Table 7. Mean logMAR BCVA before and after treatment in Eyes with and without Choroidal Vascular Hyperpermeability

	Treatment (*n*)	Baseline	3-Month Follow-up	*P* Value (*t*-test)
With choroidal hyperpermeability	PDT + IVR (6)	0.46 ± 0.28	0.34 ± 0.39	0.314
	Mono-IVR (20)	0.41 ± 0.36	0.33 ± 0.33	0.040
Without choroidal hyperpermeability	PDT + IVR (10)	0.76 ± 0.55	0.64 ± 0.59	0.226
	Mono-IVR (43)	0.49 ± 0.43	0.42 ± 0.41	0.014

Treatment consisted of intravitreal ranibizumab monotherapy or PDT combined with intravitreal ranibizumab. IVR, intravitreal ranibizumab.

ranibizumab, the mean subfoveal choroidal thickness was decreased in both typical AMD and PCV. Taken together, PDT leads to choroidal thinning not only in PCV but also in typical AMD eyes, whereas intravitreal ranibizumab has less effect on choroidal thickness in these diseases. These findings may be reflective of the different treatment effects of PDT on typical AMD and PCV.[3,7] Choroidal thickness is lower in typical AMD than that in PCV; thus, additional thinning of the choroid after PDT may have adverse effects and influence visual prognosis, especially in typical AMD.

Existing evidence suggests an association between AMD and polymorphisms in the *CFH* and *ARMS2* genes.[32–35] In a Japanese cohort, we have shown that three single nucleotide polymorphisms of *CFH* Y402H, I62V, and *ARMS2* A69S are associated with typical AMD and PCV.[36] However, possible associations between choroidal thickness and genetic background remained unknown. In the present study, the I62V polymorphism in the *CFH* gene seemed to contribute to choroidal thickness in patients with PCV. *CFH* expression has been shown to occur primarily in the RPE, drusen, and choroidal capillaries.[32] *CFH* is a critical negative regulator of

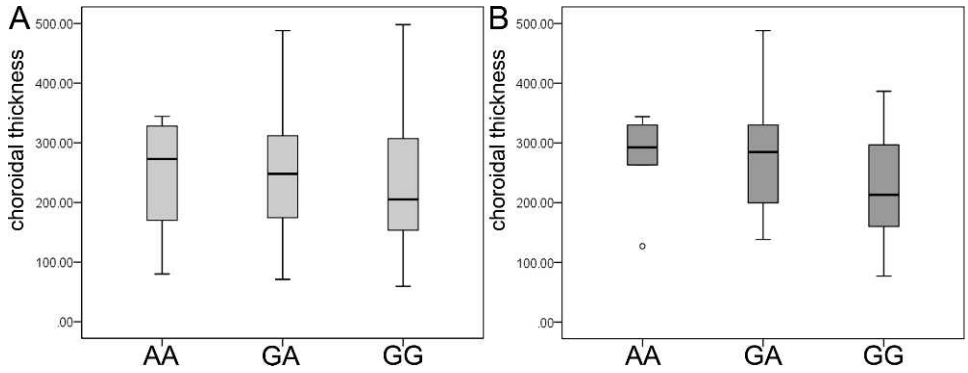

Figure 6. Subfoveal choroidal thickness and I62V polymorphism in the complement factor H gene. (**A**) Eyes with typical AMD and PCV. Mean choroidal thickness was 247.5 ± 97.7 μm in genotype AA, 248.2 ± 97.6 μm in genotype GA, and 221.9 ± 102.7 μm in genotype GG. (**B**) Eyes with PCV. Mean choroidal thickness was 274.9 ± 79.0 μm in genotype AA, 273.9 ± 99.2 μm in genotype GA, and 219.5 ± 90.0 μm in genotype GG.

Table 8. Distribution of *ARMS2* A69S, *CFH* I62V, and *CFH* Y402 Genotypes in Patients with and without Choroidal Hyperpermeability

	Hyperpermeability (+)					Hyperpermeability (−)					
	Genotype, No. (%)			Allele, No. (%)		Genotype, No. (%)			Allele, No. (%)		*P* *
ARMS2 A69S	GG	GT	TT	G	T	GG	GT	TT	G	T	
	6 (19)	15 (47)	11 (34)	27 (42)	37 (58)	7 (13)	22 (41)	25 (46)	36 (33)	72 (67)	0.244
CFH I62V	AA	GA	GG	A	G	AA	GA	GG	A	G	
	5 (16)	11 (35)	15 (48)	21 (34)	41 (66)	4 (7)	18 (33)	32 (59)	26 (24)	82 (76)	0.169
CFH Y402	CC	CT	TT	C	T	CC	CT	TT	C	T	
	1 (3)	5 (16)	26 (81)	7 (11)	57 (89)	1 (2)	13 (24)	40 (74)	15 (14)	93 (86)	0.575

*P value from allelic χ^2 test 2 × 2 table for its exact counterpart. *ARMS2*, age-related maculopathy susceptibility 2; *CFH*, complement factor H.

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the alternative pathway of the complement system.[32] The association between *CFH* and choroidal thickness in PCV leads to the hypothesis that inflammation may be involved in the choroidal thickness changes in PCV. A histopathologic study demonstrated infiltration of T and B lymphocytes present throughout the choroid in an eye with PCV and infiltration of macrophages among PCV lesions,[37] suggesting that inflammation is implicated in the pathogenesis of PCV. Further genetic study in a large cohort should deepen our understanding of the clinical significance of choroidal thickness and choroidal hyperpermeability, which may be involved in the pathology of typical AMD and PCV.

This study has some limitations. In addition to the retrospective nature of the study and lack of controls, the choroidal thickness in all images was evaluated manually because no automated computer software is available to calculate choroidal thickness. Although EDI-OCT increases the sensitivity of the choroid, light scattering by the RPE and choroid still occurs; this hampers visualization of the choriosclera interface in some patients, especially in eyes with a very thick choroid. In such eyes, 5–10 points at which the choriosclera interface could be identified were chosen and connected to form a segmentation line, and the subfoveal choroidal thickness was measured. Despite these limitations, we found that choroidal thickness was associated with subtypes of AMD, choroidal hyperpermeability, and polymorphisms in the *CFH* gene. Choroidal thickness was greater in PCV than that in typical AMD. Choroidal thickness was greater in eyes with choroidal hyperpermeability, both in typical AMD and PCV, and both in disease eyes and fellow eyes. In eyes without choroidal hyperpermeability, EDI-OCT is useful as an auxiliary measure for differentiating typical AMD and PCV. PDT combined with intravitreal ranibizumab decreased the choroidal thickness both in typical AMD and PCV; thus, a lengthy follow-up study is needed for evaluating this combined therapy. Further research on the association of inflammation and choroidal structure will deepen our understanding of the pathology of these diseases.

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