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Title: Thickness of photoreceptor layers in polypoidal choroidal vasculopathy and central serous chorioretinopathy

Article Type: Retinal Disorders

Keywords: Central serous chorioretinopathy; Optical coherence tomography; Polypoidal choroidal vasculopathy; Photoreceptor inner segment; Photoreceptor outer segment

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Abstract: Background: To evaluate retinal thickness using spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise in eyes with polypoidal choroidal vasculopathy (PCV) compared to those with normal eyes and central serous chorioretinopathy (CSC).
Methods: We retrospectively reviewed cases of foveal serous retinal detachment in 36 eyes of 36 patients with active CSC and 23 eyes of 23 patients with active PCV, and 44 eyes of 44 normal subjects. Patients were examined using SD-OCT with reduced speckle noise, and the thickness of the outer nuclear layer (ONL), photoreceptor inner segment (IS), and photoreceptor outer segment (OS) were measured.
Results: The ONL and IS were thicker in normal eyes than in eyes with CSC or PCV ($P < 0.001$). The OS was significantly less thick in eyes with PCV than in normal eyes ($P < 0.001$), whereas there was no significant difference between eyes with CSC and normal eyes. The thickness of IS and OS in eyes with PCV was related to fibrin or hemorrhage being present in the subretinal space. In eyes with PCV, best-corrected visual acuity at baseline correlated with IS thickness ($P = 0.023$).
Conclusions: Thinning of each photoreceptor layer was observed in the eyes of PCV patients as compared to that observed in the case of normal individuals. The differentiating factors between PCV and CSC, observed using SD-OCT, include the thinning of the OS in eyes with PCV, which makes SD-OCT helpful in differentiating PCV from CSC. More severe photoreceptor alterations were seen in PCV because fibrin and hemorrhage were present in the subretinal space, which correlated with poorer vision.

January 29.2010

Dr. Bernd Kirchhof, M.D.
Editor-in-Chief
Graefe's Archive for Clinical and Experimental Ophthalmology

Ref.: GRAEFES-D-09-00690
Thickness of photoreceptor layers in polypoidal choroidal vasculopathy and central serous chorioretinopathy

Dear Dr. Kirchhof:

We deeply appreciate the review of our manuscript and thank you for forwarding to us the excellent comments. We are resubmitting our revised manuscript after having carefully considered the points made and after having altered the manuscript according to the suggestions. We believe that we have responded to all of the comments and hope that you now find this paper suitable for publication in ***Graefe's Archive for Clinical and Experimental Ophthalmology***
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Yours sincerely,

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January 28.2010

Dr. Bernd Kirchhof, M.D.
Editor-in-Chief
Graefe's Archive for Clinical and Experimental Ophthalmology

Dear Dr. Kirchhof:

Thank you very much for your letter dated January 16, 2009, in response to our manuscript (GRAEFES-D-09-00690) titled " **Thinning of photoreceptor layers in polypoidal choroidal vasculopathy and central serous chorioretinopathy**" and for forwarding the comments of the reviewer. We appreciate your review of our manuscript and are grateful for the many constructive suggestions, which have greatly improved our manuscript. We have carefully considered all the comments and made revisions accordingly. We have responded to all of the comments and hope that you will find our revised manuscript suitable for publication in ***Graefe's Archive for Clinical and Experimental Ophthalmology***.

Yours sincerely,

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Our revisions made in accordance with the reviewer's suggestions are as follows:

Reviewers' comments:
Reviewer #3: The authors state, that they want to examine the retinal structure in eyes with PCV and foveal SRD as compared to eyes with CSC. Moreover, in the conclusion section of the abstract they state: "The differentiating factors between PCV and CSC, observed using SD-OCT, include the thinning of the IS and OS in eyes with PCV, which makes SD-OCT helpful in differentiating PCV from CSC."
Now my first question is, why a "normal group" is necessary to support these statements.

We would like to clarify the thinning of each photoreceptor layer in the eyes of patients with PCV by comparing these layers with those in normal individuals. Thus, we have revised the Abstract, Introduction, and Discussion as follows.

The following text was added in the Abstract: (Page 3, line 2-5, 19-20)

"To evaluate retinal thickness using spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise in eyes with polypoidal choroidal vasculopathy (PCV) compared to those with normal eyes and central serous chorioretinopathy (CSC)."

"Thinning of each photoreceptor layer was observed in the eyes of PCV patients as compared to that observed in the case of normal individuals."

The following changes were incorporated in the Introduction: (Page 6, line 9-11)

"In this study, we used the SD-OCT system with reduced speckle noise to examine the retinal structure in eyes with PCV and foveal SRD as compared to normal eyes or eyes with CSC and foveal SRD."

The following text was included in the Discussion: (Page 16, line 5-10)

"In conclusion, SD-OCT with reduced speckle noise allows detailed observation of retinal structures. Using SD-OCT, we found thinning of each photoreceptor layer in eyes with PCV compared to normal eyes, and the thinning of the OS in eyes with PCV to be a differentiating factor between PCV and CSC; thus, SD-OCT is helpful in differentiating CSC from PCV."

Second, the authors state that PCV is commonly found in individuals over 60 whereas CSC is usually found in younger individuals. So the differentiation between PCV and CSC should be easy based on the age. In other words: why is there a need for other differentiation-criteria. However, if there is a group of patients with matched ages, it makes sense to differentiate between PCV and CSC. This argumentation could be extended to other observable and not observable factors, which differ between the comparison groups and may have an effect on the retinal thickness. Thus I am not very satisfied to present the results of the stratified analysis as online material only. Further your data table 1 shows, that not only age but also fibrin, subretinal hemorrhage and baseline logMar differ between the comparison groups. In an explorative analysis and model building approach it is likely to include all effects with a (univariate) p-value below 0.25 in the model, i.e. additionally follow up period and distance from fovea.
By the way, I have trouble with the authors reply, that they found similar results in individuals over 60 years, based on their table 3 and subtable 1.

We thank reviewer #3 for commenting on the inappropriate use of the method of

stratified analysis. We examined patients who were above 60 years old and did not exhibit fibrin or hemorrhage in the subretinal space (Supplemental Table1). The subgroups did not significantly differ in terms of age, results of the follow-up time, area of serous retinal detachment, and baseline logMAR visual acuity. The thickness of the OS layer was significantly lower in the case of PCV patients than in that of the CSC patients; the results are consistent with those presented in Table 3. However, the thickness of the IS layer did not differ significantly between the PCV and CSC patients; thus, we have revised the Title, Abstract, Results, and Discussion as follows.

The following revisions were made in the Title:

“Thinning” was changed to “thickness” because in eyes with CSC OS thickness was higher in Supplemental Table1.

The following revisions were made in the Abstract: (Page 3, line 20-22)

“The differentiating factors between PCV and CSC, observed using SD-OCT, include the thinning of the OS in eyes with PCV, which makes SD-OCT helpful in differentiating PCV from CSC.”

The following revisions were made in the Results: (Page 11, line 9-21)

“The thickness of the ONL, IS, and OS layers in each group was examined only in individuals who were more than 60 years old and did not exhibit fibrin or hemorrhage in the subretinal space (Supplemental Table 1). On comparison with the normal individuals, the CSC and PCV patients exhibited thinning of the ONL and IS layers; however, the difference in the thickness of the IS layer between the CSC and PCV patients was not significant. Compared with the normal individuals, the CSC patients exhibited a significant increase and the PCV patients exhibited a significant decrease in the thickness of the OS layer. The mean $\pm$ SD age (in years) of the individuals in these subgroups did not significantly differ (normal individuals, 68 $\pm$ 6; CSC patients, 67 $\pm$ 9; and PCV patients, 72 $\pm$ 8). In addition, the mean follow-up period, mean distance from the fovea to the nearest point of attachment to the retina, and mean baseline logMAR score ($P = 0.414$, 0.244, and 0.359, respectively; Tukey-Kramer test) did not significantly differ among the subgroups.”

The following revisions were made in the Discussion: (Page 13, line17-Page 15, line8)

“The changes in the thickness of the IS layer may be caused by SRD, fibrin deposition, or hemorrhage. In our study, the thickness of the IS layer was significantly lower in the CSC or PCV patients than in the normal individuals. Thickness of the IS layer did not significantly differ between the CSC and PCV in

age-matched patients who did not exhibit fibrin deposition or hemorrhage in the subretinal space; therefore, we think that the changes in the thickness of the IS layer may be attributable mainly to the SRD. However, the thickness of the IS layer was significantly lower in the case of PCV patients who exhibited fibrin or hemorrhage than in the case of those who did not exhibit these abnormalities. Fibrin deposition or hemorrhage are frequently observed in the subretinal fluid in the case of PCV patients; this and possibly other factors might cause further damage to the IS layer, resulting in poor vision."

"The thickness of the OS layer significantly differed between the PCV and CSC patients. The thickness of the OS layer was significantly lower in the case of PCV patients than in that of normal individuals. However the thickness of the OS layer did not significantly differ between the CSC patients and normal individuals. In the age-matched patients who did not exhibit fibrin deposition or hemorrhage, the thickness of the OS layer was higher in the CSC patients and lower in the case of PCV patients than in that of normal individuals. Matsumoto et al reported elongation of the OS in the eyes of patients with CSC [21]. We found that the OS was frequently elongated in the eyes of the CSC patients; however, this phenomenon may be rare in PCV patients. Thus, the OS in the eyes of CSC patients may elongate until the OSs and RPE are reattached; however, elongation of the OS is not observed in the case of PCV patients. The presence of fibrin or hemorrhage in the subretinal space might have directly damaged the OS in the eyes of the PCV patients, as indicated by our finding that the thickness of the OS layer was significantly lower in the case of patients who exhibited fibrin or hemorrhage than in the case of those who did not exhibit these abnormalities. However, the thickness of the OS layer was decreased even in the case of PCV patients who did not exhibit fibrin or hemorrhage. On the basis of these findings, we postulate 2 hypotheses. First, other factors that possibly exist in the subretinal fluid damaged the OS in the eyes of the PCV patients. Second, the damage caused to the IS layer may be more severe in the PCV patients than in the CSC patients. The OS is produced from the IS of the photoreceptors; further, in the eyes of the PCV patients, the IS in the detached fovea may be more severely damaged, resulting in the inhibition of OS elongation."

"PCV is the most common disease occurring in individuals more than 60 years old, whereas CSC occurs in both younger individuals and those above 60 years old. The clinical, FA, IA, or tomographic findings of some PCV cases are similar to those of the CSC. Thus, at times, it is difficult to differentiate CSC and PCV, especially

during diagnosis in elderly patients who do not exhibit fibrin deposition or hemorrhage. In the current study, we examined patients who were more than 60 years old and did not exhibit fibrin or hemorrhage (Supplemental Table 1). The thickness of the OS layer significantly increased in the CSC patients and significantly decreased in the PCV patients as compared to that observed in the case of normal individuals. Thus, the thickness of the OS, as measured using SD-OCT, may help in the differential diagnosis of these 2 diseases."
"Using SD-OCT, we found the thinning of the OS in eyes with PCV to be a differentiating factor between PCV and CSC; thus, SD-OCT is helpful in differentiating CSC from PCV."

I am also not very happy with the interpretation of the CV as inter-observer reproducibility measure. The authors should think about calculation of the intraclass correlation coefficient (ICC), (Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. Educational and Psychological Measurement 1973;33:613-19.)

We thank reviewer #3 for commenting on the inappropriate application of the reproducibility measurement. We have presented the ICC in Table 2 of the revised manuscript and included the following text in the Method, Results, and Discussion.
The following revisions were made in the Methods: (Page 9, line 2-3)
"The intraclass correlation coefficient (ICC) was obtained as inter-observer reproducibility measure."
The following revisions were made in the Results: (Page 10, line 7-10)
"Inter-observer reproducibility of the measurement of retinal thickness by using SD-OCT with reduced speckle noise was assessed by calculating inter-observer ICC; ICC ranged from 0.953-0.975 for the measurement of each retinal layer thickness (Table 2)."
The following revisions were made in the Discussion: (Page 12, line 25-Page 12, line2)
"In the current study, the inter-observer ICC ranged from 0.953-0.975 for the measurement of retinal thickness, suggesting that measuring the thickness of each retinal layer by using SD-OCT with reduced speckle noise has good reproducibility."

Some more detailed comments:
On p 7 Line 6 : ttest was declared for comparing patient characteristics although Tukey Kramer Test was used for comparison of age (p4 line 23). If ttest is used, significance

level should be corrected for multiple testing.

We employed the Tukey-Kramer test for comparing patient characteristics and fundus findings, and the results are presented in Table 1. (Page 9, line15, 24, Page 10, line1)

On p 7 Line 13 : The usual notation of a correlation coefficient is r. R2 has another meaning. So what is calculated on page 11 line 12.

We calculated correlation coefficient, and thus, we have now replaced "R^2" with "r^2." (Page 11, line23, Page 12, line 1,3)

Thickness of photoreceptor layers in polypoidal choroidal vasculopathy and central serous chorioretinopathy

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All authors have full control of all primary data and agree to allow Graefes Archive for Clinical and Experimental Ophthalmology to review our data upon request.

This article contains a Table as additional online-only material. The following should appear online-only: Supplemental Table 1.

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Abstract

Background: To evaluate retinal thickness using spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise in eyes with polypoidal choroidal vasculopathy (PCV) compared to those with normal eyes and central serous chorioretinopathy (CSC).

Methods: We retrospectively reviewed cases of foveal serous retinal detachment in 36 eyes of 36 patients with active CSC and 23 eyes of 23 patients with active PCV, and 44 eyes of 44 normal subjects. Patients were examined using SD-OCT with reduced speckle noise, and the thickness of the outer nuclear layer (ONL), photoreceptor inner segment (IS), and photoreceptor outer segment (OS) were measured.

Results: The ONL and IS were thicker in normal eyes than in eyes with CSC or PCV ($P < 0.001$). The OS was significantly less thick in eyes with PCV than in normal eyes ($P < 0.001$), whereas there was no significant difference between eyes with CSC and normal eyes. The thickness of IS and OS in eyes with PCV was related to fibrin or hemorrhage being present in the subretinal space. In eyes with PCV, best-corrected visual acuity at baseline correlated with IS thickness ($P = 0.023$).

Conclusions: Thinning of each photoreceptor layer was observed in the eyes of PCV patients as compared to that observed in the case of normal individuals. The differentiating factors between PCV and CSC, observed using SD-OCT, include the thinning of the OS in eyes with PCV, which makes SD-OCT helpful in differentiating PCV from CSC. More severe photoreceptor alterations were seen in PCV because fibrin and hemorrhage were present in the subretinal space, which correlated with poorer vision.

Keywords Central serous chorioretinopathy, Optical coherence tomography, Polypoidal

choroidal vasculopathy, Photoreceptor inner segment, Photoreceptor outer segment

Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by multiple terminal reddish-orange nodules and a complex network of vessels in the eye, and often causes serous retinal detachment (SRD) or pigment epithelial detachments (PEDs)[1-6]. While its pathogenesis is not yet fully understood, PCV originates in an abnormality of the inner choroidal vessels and is presumed to be a variant of choroidal neovascularization (CNV).

Central serous chorioretinopathy (CSC) is characterized by SRD in the macular area, often in association with small serous PEDs and retinal pigment epithelial atrophy [7, 8]. Evaluation using indocyanine green angiography (IA) shows multifocal staining islands in the inner choroid, suggesting that exudative changes within the inner choroid constitute the primary event in CSC [9-14].

Some cases of PCV have clinical, fluorescein angiography (FA), IA, or tomographic findings similar to those of CSC, and it is difficult to differentiate these cases from those of CSC [3-5]. Choroidal vascular hyperpermeability, a characteristic finding in CSC, might be involved in the pathogenesis of PCV, suggesting that the pathogenesis of PCV and CSC is similar in part [4]. Further, both PCV and CSC are associated with SRD. However, most CSC patients have good visual acuity (VA) despite macular detachment, whereas many PCV patients have decreased VA. The changes in retinal morphology that lead to these different visual outcomes have not been documented.

Optical coherence tomography (OCT) is the primary technique for studying both PCV and CSC. OCT has recently evolved into spectral-domain OCT (SD-OCT), which has 43–100 times higher imaging speeds than time-domain OCT (TD-OCT) as well as a much higher signal-to-noise ratio [15-17]. A new SD-OCT instrument, the Spectralis™ HRA+OCT (Heidelberg Engineering, Dossenheim, Germany), combines confocal

scanning laser ophthalmoscopy and SD-OCT. It also allows the integration of information obtained from FA, IA, and SD-OCT, thus enabling the determination of the exact site of origin of a disease. Additionally, this new instrument uses an eye-tracking system to eliminate motion artifacts, which limit the detection of small changes in the eye. Combining eye tracking with multiple B-scan averaging [18] permits the production of finely detailed images of all retinal layers with reduced speckle noise. These technological advances enable more accurate measurements of each retinal layer, and should help to differentiate between the pathologic features of CSC and PCV.

In this study, we used the SD-OCT system with reduced speckle noise to examine the retinal structure in eyes with PCV and foveal SRD as compared to normal eyes or eyes with CSC and foveal SRD. We also studied the changes in fine structural factors, such as the thickness of the outer nuclear layer (ONL), photoreceptor inner segment (IS), and photoreceptor outer segment (OS), to determine the association between structural changes and visual function.

Subjects and Methods

For this observational case study, we retrospectively reviewed 44 eyes of 44 normal subjects (36 men and 8 women) as controls, 36 eyes of 36 patients with active CSC (31 men and 5 women) and 23 eyes of 23 patients with active PCV (17 men and 6 women) (Table 1). We enrolled PCV and CSC patients who visited the Macular Service in Kyoto University Hospital, Kyoto, Japan, for the first time between November 2007 and March 2009. All patients were Japanese. The mean age of normal subjects was 68.2 (range, 49–84 years); that of CSC patients, 49.0 (range, 37–73 years) (compared to normal subjects, $P < 0.001$, Tukey-Kramer test); and that of PCV patients, 71.3 (range, 57–92 years) (compared to normal subjects, $P = 0.345$, Tukey-Kramer test). The duration of symptoms ranged from 2 weeks to 4 years (median, 3.0 months) for CSC

and from 1 month to 6 years (median, 3.0 months) for PCV. Eight eyes had recurrent CSC and 6, chronic CSC (defined as SRD wherein the duration of symptoms was more than 6 months). Only eyes with active CSC or active PCV that had foveal SRD were included. Eyes with a history of photocoagulation, photodynamic therapy, or vitreous surgery were excluded. All investigations adhered to the tenets of the Declaration of Helsinki, and the current study was approved by the institutional review board and the ethics committee at Kyoto University Graduate School of Medicine.

All patients underwent a comprehensive ophthalmologic examination, including assessment of best-corrected VA (BCVA) and intraocular pressure, and assessment using indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, fundus photography, and simultaneous FA and IA with a confocal laser scanning system (Spectralis™ HRA+OCT).

The diagnosis of CSC or PCV was based on fundus photograph, FA, and IA. In eyes with PCV, IA shows a branching vascular network terminating in either a single polyp or a cluster of multiple polyps. In most cases, reddish-orange nodules observed by ophthalmoscopic examination correspond to the polypoidal lesion seen by IA. In eyes with CSC, FA shows leakage from the RPE, and IA shows an absence of polypoidal choroidal vascular lesions. 2 macular experts (NY and AT) examined all the acquired color fundus photographs, FA, and IA. They worked independently. When their evaluations did not agree, the opinion of a third observer (SO) was invited and the results were discussed until consensus was reached.

Retinal imaging was performed using the Spectralis™ HRA+OCT. First, horizontal and vertical line scans through the fovea centralis were obtained at a 30^{o} angle, followed by 12 radial scans (6 mm) centered at the fovea; finally, 19 serial horizontal scans (6 mm) were obtained. At each location of interest on the retina, 12~50 SD-OCT images were acquired and averaged to reduce speckle noise.

Using these SD-OCT images, we analyzed the morphologic changes in the retina in eyes with CSC or PCV. To measure the thickness of the intraretinal structures in normal eyes and eyes with CSC or PCV, we chose 3~5 B-scan images with the deep foveal depression from the vertical, horizontal, and radial scans of the fovea. These B-scan images were sent to the Kyoto University OCT Reading Center at the Kyoto University Graduate School of Medicine (Kyoto, Japan). By using the digital caliper tool built into the SD-OCT system with reduced speckle noise, retinal thickness was then measured by 2 independent experienced observers (MY and AH) who were unaware of the diagnosis or other clinical information regarding the eyes. The thickness of each retinal layer was the mean thickness determined using these B-scan images.

At the fovea, we measured the thickness of the ONL, which is approximately the distance between the outer border of the internal limiting membrane (ILM) and external limiting membrane (ELM); IS, which is approximately the distance between the ELM and the inner border of the junction between the IS and OS (IS/OS); and OS. In an attached retina, the thickness of the OS is approximately the distance between the inner borders of the IS/OS and retinal pigmented epithelium (RPE). In a detached retina, the thickness of the OS is approximately the distance between the inner border of the IS/OS and the tip of the OS.

Patients underwent BCVA and fundus assessment and SD-OCT examination at every visit. Intravitreal bevacizumab or photodynamic therapy combined with intravitreal triamcinolone acetonide and intravitreal bevacizumab was given to 11 and 5 eyes with PCV, respectively, and photocoagulation or photodynamic therapy was performed in 3 and 5 eyes with CSC, respectively, during the follow-up period.

BCVA measured using the Landolt Chart was expressed as the logarithm of minimal angle of resolution (logMAR) for statistical calculation. For comparing the

patient characteristic variables, Tukey-Kramer test and Fisher's exact test were used. The intraclass correlation coefficient (ICC) was obtained as inter-observer reproducibility measure. For comparing the differences in retinal thickness between normal eyes and eyes with CSC or PCV, Tukey-Kramer test was used. For comparing the differences in retinal thickness between eyes with fibrin or subretinal hemorrhage and those without it, an unpaired *t*-test was used. We used the Spearman rank correlation coefficient to study the association between BCVA and the thickness of the ONL, IS, or OS. All statistical evaluations were performed using a commercially available software program (SPSS17; SPSS Inc., Chicago, IL). *P* less than 0.05 was considered statistically significant.

Results

For this study, we selected eyes with foveal SRD and CSC or PCV. The height or area of SRD did not significantly differ between eyes with CSC and PCV (*P* = 0.971 for height and 0.090 for area, Tukey-Kramer test). Fibrin was observed in the subretinal space in 7 of the 36 eyes with CSC (19%) and 13 of the 23 eyes (57%) with PCV (*P* = 0.001, Fisher's exact test). Subretinal hemorrhage was not seen in any eye with CSC, but it was observed in 15 eyes with PCV (65%; *P* < 0.001, Fisher's exact test). At last follow-up, foveal SRD resolved in 23 eyes with CSC (64%) and 15 eyes with PCV (65%) (*P* = 0.918, Fisher's exact test) (Table 1).

The mean BCVA at the baseline was 0.75 (range, 0.06–1.5; 0.13 logMAR) for eyes with CSC and 0.44 (range, 0.02–1.5; 0.36 logMAR) for eyes with PCV. Thus, at the baseline, eyes with CSC had better BCVA than those with PCV (*P* = 0.006, Tukey-Kramer test). The mean BCVA at last follow-up was 0.87 (range, 0.06–1.5; 0.06 logMAR) for eyes with CSC and 0.52 (0.28 logMAR; range, 0.04–1.5) for eyes with PCV; therefore, eyes with CSC had better BCVA than eyes with PCV at the last

follow-up as well (*P* = 0.007,Tukey-Kramer test).

The images obtained using SD-OCT with reduced speckle noise showed 4 highly reflective lines in each normal eye, namely the ELM, the IS/OS, an intermediate reflective line between IS/OS and RPE, and the RPE (Fig 1). In each eye with CSC or PCV, the detached retina showed the ELM, and the IS/OS lines, but not the intermediate reflective line (Figs 2–4).

Inter-observer reproducibility of the measurement of retinal thickness by using SD-OCT with reduced speckle noise was assessed by calculating inter-observer ICC; ICC ranged from 0.953-0.975 for the measurement of each retinal layer thickness (Table 2).

At the central fovea, the mean ONL thickness was significantly lower in eyes with CSC or PCV than in normal eyes (*P* < 0.001, Tukey-Kramer test) (Table 3). In contrast, the mean ONL thickness did not differ between eyes with CSC and PCV (*P* = 0.998, unpaired *t*-test), and this was also observed at the last follow-up (*P* = 0.747, unpaired *t*-test).

At the initial examination, the mean IS thickness was significantly lower in eyes with CSC or PCV than in normal eyes (*P* < 0.001, Tukey-Kramer test) (Table 3). Moreover, the IS thickness was significantly lower in eyes with PCV than in those with CSC (*P* = 0.034, Tukey-Kramer test). The IS thickness at the last follow-up was significantly lower in eyes with PCV than in those with CSC (*P* = 0.018, unpaired *t*-test).

At the central fovea, the mean OS thickness was significantly lower in eyes with PCV than in normal eyes (*P* < 0.001, Tukey-Kramer test), whereas there was no significant difference between the OS thickness in eyes with CSC and normal eyes (*P* = 0.394, Tukey-Kramer test) (Table 3). The elongation of the OS (>60 μm) was observed in 17 of the 36 eyes with CSC (47%). In contrast, this elongated OS was observed only in 2 of the 23 eyes with PCV (9%; *P* = 0.002, Fisher's exact test). At the last

follow-up, the mean OS thickness was significantly lower in eyes with PCV than in those with CSC ($P = 0.004$, unpaired *t*-test).

The thickness of IS and OS in eyes with PCV was related to the presence of fibrin or hemorrhage in the subretinal space (Table 4, Fig. 4). The thickness of IS and OS in eyes with fibrin or hemorrhage was significantly lower than that in eyes without fibrin or hemorrhage ($P = 0.001$ and 0.022, respectively, unpaired *t*-test). Moreover, BCVA was significantly worse in eyes with fibrin or hemorrhage than in eyes without it ($P = 0.035$, unpaired *t*-test). The ONL thickness was not related to fibrin or hemorrhage.

The thickness of the ONL, IS, and OS layers in each group was examined only in individuals who were more than 60 years old and did not exhibit fibrin or hemorrhage in the subretinal space (Supplemental Table 1). On comparison with the normal individuals, the CSC and PCV patients exhibited thinning of the ONL and IS layers; however, the difference in the thickness of the IS layer between the CSC and PCV patients was not significant. Compared with the normal individuals, the CSC patients exhibited a significant increase and the PCV patients exhibited a significant decrease in the thickness of the OS layer. The mean $\pm$ SD age (in years) of the individuals in these subgroups did not significantly differ (normal individuals, 68 ± 6; CSC patients, 67 ± 9; and PCV patients, 72 ± 8). In addition, the mean follow-up period, mean distance from the fovea to the nearest point of attachment to the retina, and mean baseline logMAR score did not significantly differ among the subgroups ($P = 0.414$, 0.244, and 0.359, respectively; Tukey-Kramer test).

In eyes with CSC, the logMAR BCVA at the baseline correlated with ONL thickness ($P = 0.003$, $r^2 = 0.23$) and IS thickness ($P = 0.022$, $r^2 = 0.14$), although there was no correlation between logMAR BCVA and OS, and this was the case even at the last follow-up ($P = 0.002$ for ONL thickness and $P < 0.001$ for IS thickness).

In eyes with PCV, the logMAR BCVA at the baseline correlated with IS thickness

(P = 0.023, r^2 = 0.22); it weakly correlated or did not correlate with OS thickness (P = 0.075). At the last follow-up, logMAR BCVA correlated with IS thickness (P = 0.001, r^2 = 0.44) and OS thickness (P = 0.033, r^2 = 0.38).

Discussion

OCT has provided a better understanding of the mechanisms underlying the development of both CSC and PCV [19-29]. The use of TD-OCT showed increased thickening and granularity of the outer photoreceptor layer in the SRD area in eyes with CSC [19, 20]. Using SD-OCT, Matsumoto et al showed that the OS was elongated and that ONL thickness was decreased in eyes with CSC [21]. Ojima et al found that a large defect in the inner and outer segments of foveal photoreceptors correlated with poor VA [22]. OCT imaging of eyes with PCV revealed sharp protrusions of the RPE with moderate inner reflectivity; the protrusions were associated with reddish-orange nodules seen on fundus photography [23, 24]. In eyes with PCV, a double-layered line at the RPE level was found to be associated with a branching vascular network [25]. To date, however, limited information is available on the retinal structures in eyes with PCV, and the different morphological changes in the retina in CSC or PCV have not been documented in detail.

The clinical utility of any instrument depends on the reproducibility of the measurements obtained with it. A new SD-OCT with reduced speckle noise, the Spectralis™ HRA+OCT, eliminates motion artifacts, which limit the detection of small changes in the eye, using an eye-tracking system. These technological advances enable more accurate and reproducible measurement of each retinal layer. In fact, Wolf-Schnurrbusch et al reported that Spectralis™ HRA+OCT had the best measurement repeatability among 6 different OCT instruments [30]. In the current study, the inter-observer ICC ranged from 0.953-0.975 for the measurement of retinal

thickness, suggesting that measuring the thickness of each retinal layer by using SD-OCT with reduced speckle noise has good reproducibility.

In normal eyes, the mean thickness of the ONL, IS, and OS was 126, 30, and 56 μm, respectively; these values are consistent with those obtained by Matsumoto et al using SD-OCT (135, 35, and 60 μm, respectively) [21]. Yamada, in a histological study of a human eye (the surgically enucleated eye of a 45-y-old woman), reported that at the fovea, the distance between the ILM and ELM was 150 μm, and at the central fovea, the thickness of the IS and OS was approximately 20–30 μm and 45 μm, respectively [31]. Thus, retinal thickness measured by SD-OCT was identical with that obtained by studying histological sections.

We hypothesize that SRD may cause thinning of the ONL. ONL thickness was significantly lower in eyes with CSC or PCV than in normal eyes, which is consistent with the findings of Matsumoto et al, who reported that ONL thickness was decreased in eyes with CSC [21]. The thickness of the ONL might reflect, at least in part, the volume of the photoreceptors, and so, a reduction in ONL thickness suggests that the volume of the photoreceptors decreases in detached retinas in eyes with CSC or PCV.

The changes in the thickness of the IS layer may be caused by SRD, fibrin deposition, or hemorrhage. In our study, the thickness of the IS layer was significantly lower in the CSC or PCV patients than in the normal individuals. Thickness of the IS layer did not significantly differ between the CSC and PCV in age-matched patients who did not exhibit fibrin deposition or hemorrhage in the subretinal space; therefore, we think that the changes in the thickness of the IS layer may be attributable mainly to the SRD. However, the thickness of the IS layer was significantly lower in the case of PCV patients who exhibited fibrin or hemorrhage than in the case of those who did not exhibit these abnormalities. Fibrin deposition or hemorrhage are frequently observed in the subretinal fluid in the case of PCV patients; this and possibly other factors might cause

further damage to the IS layer, resulting in poor vision.

The thickness of the OS layer significantly differed between the PCV and CSC patients. The thickness of the OS layer was significantly lower in the case of PCV patients than in that of normal individuals. However the thickness of the OS layer did not significantly differ between the CSC patients and normal individuals. In the age-matched patients who did not exhibit fibrin deposition or hemorrhage, the thickness of the OS layer was higher in the CSC patients and lower in the case of PCV patients than in that of normal individuals. Matsumoto et al reported elongation of the OS in the eyes of patients with CSC [21]. We found that the OS was frequently elongated in the eyes of the CSC patients; however, this phenomenon may be rare in PCV patients. Thus, the OS in the eyes of CSC patients may elongate until the OSs and RPE are reattached; however, elongation of the OS is not observed in the case of PCV patients. The presence of fibrin or hemorrhage in the subretinal space might have directly damaged the OS in the eyes of the PCV patients, as indicated by our finding that the thickness of the OS layer was significantly lower in the case of patients who exhibited fibrin or hemorrhage than in the case of those who did not exhibit these abnormalities. However, the thickness of the OS layer was decreased even in the case of PCV patients who did not exhibit fibrin or hemorrhage. On the basis of these findings, we postulate 2 hypotheses. First, other factors that possibly exist in the subretinal fluid damaged the OS in the eyes of the PCV patients. Second, the damage caused to the IS layer may be more severe in the PCV patients than in the CSC patients. The OS is produced from the IS of the photoreceptors; further, in the eyes of the PCV patients, the IS in the detached fovea may be more severely damaged, resulting in the inhibition of OS elongation.

PCV is the most common disease occurring in individuals more than 60 years old, whereas CSC occurs in both younger individuals and those above 60 years old. The clinical, FA, IA, or tomographic findings of some PCV cases are similar to those of the

CSC. Thus, at times, it is difficult to differentiate CSC and PCV, especially during diagnosis in elderly patients who do not exhibit fibrin deposition or hemorrhage. In the current study, we examined patients who were more than 60 years old and did not exhibit fibrin or hemorrhage (Supplemental Table 1). The thickness of the OS layer significantly increased in the CSC patients and significantly decreased in the PCV patients as compared to that observed in the case of normal individuals. Thus, the thickness of the OS, as measured using SD-OCT, may help in the differential diagnosis of these 2 diseases.

Thinning of the photoreceptor layer may lead to a reduction in VA. Recently, Matsumoto et al reported that decreased ONL thickness correlates with worse BCVA in eyes with CSC, which is in agreement with our results [32]. Moreover, in the current study, BCVA correlated with the IS thickness at baseline and the last visit, suggesting that the thickness of ONL and IS may be important for visual prognosis in eyes with CSC. On the other hand, thinning of IS and/or OS correlated with worse BCVA in eyes with PCV although the observed correlation was rather weak. Thus, IS thickness may be a common indicator for visual outcomes in CSC and PCV.

We believe that the ELM may act as a barrier for the spread of fibrin or hemorrhage. The zonula adherens between the Müller cells and the photoreceptors at the base of the OS, which make up the ELM, have a very narrow angle [33]. They are not sealed, as are the zonula occludens of the RPE and retinal capillaries, but they do limit the movement of large molecules. Large molecules do not diffuse freely across the retina as they are partially blocked by the ELM [33]. Accordingly, it is reasonable to suppose that the IS and OS are likely to be damaged by fibrin products or hemorrhage in the subretinal space, although these products have a lower influence on the ONL. This may explain why the thickness of the ONL did not differ between eyes with PCV and CSC, whereas that of the IS and OS was lower in eyes with PCV than in eyes with

CSC. In eyes with PCV, plasma constituents and exudative products are frequently found in the subretinal fluid, which may disturb the IS and OS. If the inner segments are disturbed, the photoreceptors may be irreversibly altered, which can influence visual function.

In conclusion, SD-OCT with reduced speckle noise allows detailed observation of retinal structures, and thus helps to differentiate between the pathologic features of CSC and PCV. Using SD-OCT, we found thinning of each photoreceptor layer in eyes with PCV compared to normal eyes, and the thinning of the OS in eyes with PCV to be a differentiating factor between PCV and CSC; thus, SD-OCT is helpful in differentiating CSC from PCV. As compared to CSC, the photoreceptor alterations in PCV were found to be more severe because of the presence of fibrin and hemorrhage in the subretinal space, which correlated with poorer vision.

Acknowledgements/Disclosure

We wish to thank the imaging specialists of Kyoto University OCT Reading Center (Mayumi Yoshida and Akiko Hirata) for measuring retinal thickness.

References

1. Yannuzzi LA, Sorenson J, Spaide RF, Lipson B (1990) Idiopathic polypoidal choroidal vasculopathy (IPCV). Retina 10:1-8.
2. Yannuzzi LA, Wong DW, Sforzolini BS, Goldbaum M, Tang KC, Spaide RF, Freund KB, Slakter JS, Guyer DR, Sorenson JA, Fisher Y, Maberley D, Orlock DA (1999) Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol 117**:**1503-1510.
3. Yannuzzi LA, Ciardella A, Spaide RF, Rabb M, Freund KB, Orlock DA (1997) The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. Arch Ophthalmol 115:478-485.
4. Sasahara M, Tsujikawa A, Musashi K, Gotoh N, Otani A, Mandai M, Yoshimura N (2006) Polypoidal choroidal vasculopathy with choroidal vascular hyperpermeability. Am J Ophthalmol 142:601-607.
5. Yannuzzi LA, Freund KB, Goldbaum M, Scassellati-Sforzolini B, Guyer DR, Spaide RF, Maberley D, Wong DW, Slakter JS, Sorenson JA, Fisher YL, Orlock DA (2000) Polypoidal choroidal vasculopathy masquerading as central serous chorioretinopathy. Ophthalmology 107:767-777.
6. Moorthy RS, Lyon AT, Rabb MF, Spaide RF, Yannuzzi LA, Jampol LM (1998) Idiopathic polypoidal choroidal vasculopathy of the macula. Ophthalmology 105:1380-1385.
7. Yannuzzi LA, Shakin JL, Fisher YL, Altomonte MA (1984) Peripheral retinal detachments and retinal pigment epithelial atrophic tracts secondary to central serous pigment epitheliopathy. Ophthalmology 91:1554-1572.
8. Levine R, Brucker AJ, Robinson F (1989) Long-term follow-up of idiopathic central serous chorioretinopathy by fluorescein angiography. Ophthalmology 96:854-859.
9. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D (1994) Digital

indocyanine green videoangiography of central serous chorioretinopathy. Arch Ophthalmol 112:1057-1062.

10. Piccolino FC, Borgia L (1994) Central serous chorioretinopathy and indocyanine green angiography. Retina 14:231-242.
11. Scheider A, Nasemannn JE, Lund OE (1993) Fluorescein and indocyanine green angiographies of central serous choroidopathy by scanning laser ophthalmoscopy. Am J Ophthalmol 115:50-56.
12. Prunte C, Flammer J (1996) Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 121:26-34.
13. Iida T, Kishi S, Hagimura N, Shimizu K (1999) Persistent and bilateral choroidal vascular abnormalities in central serous chorioretinopathy. Retina 19:508-512.
14. Fujimoto H, Gomi F, Wakabayashi T, Sawa M, Tsujikawa M, Tano Y (2008) Morphologic changes in acute central serous chorioretinopathy evaluated by Fourier-domain optical coherence tomography. Ophthalmology 115:1494-1500.
15. Wojtkowski M, Srinivasan V, Fujimoto JG, Ko T, Schuman JS, Kowalczyk A, Duker JS (2005) Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. Ophthalmology 112:1734-1746.
16. Hangai M, Ojima Y, Gotoh N, Inoue R, Yasuno Y, Makita S, Yamanari M, Yatagai T, Kita M, Yoshimura N (2007) Three-dimensional imaging of macular holes with high-speed optical coherence tomography. Ophthalmology 114:763-773.
17. Ooto S, Hangai M, Sakamoto A, Tomidokoro A, Araie M, Otani T, Kishi S, Matsushita K, Maeda N, Shirakashi M, Abe H, Takeda H, Sugiyama K, Saito H, Iwase A, Yoshimura N (2010) Three-dimensional profile of macular retinal thickness in normal Japanese eyes. Invest Ophthalmol Vis Sci 51:465-473.
18. Sakamoto A, Hangai M, Yoshimura N (2008) Spectral-domain optical coherence

tomography with multiple B-scan averaging for speckle-noise-reduced imaging of retinal diseases. Ophthalmology 115:1071-1078.

19. Spaide RF, Klancnik JM Jr (2005) Fundus autofluorescence and central serous chorioretinopathy. Ophthalmology 112:825-833.
20. Iida T, Hagimura N, Sato T, Kishi S (2000) Evaluation of central serous chorioretinopathy with optical coherence tomography. Am J Ophthalmol 129:16-20.
21. Matsumoto H, Kishi S, Otani T, Sato T (2008) Elongation of photoreceptor outer segment in central serous chorioretinopathy. Am J Ophthalmol 145:162-168.
22. Ojima Y, Hangai M, Sasahara M, Gotoh N, Inoue R, Yasuno Y, Makita S, Yatagai T, Tsujikawa A, Yoshimura N (2007) Three-dimensional imaging of the foveal photoreceptor layer in central serous chorioretinopathy using high-speed optical coherence tomography. Ophthalmology 114:2197-2207.
23. Iijima H, Imai M, Gohdo T, Tsukahara S (1999) Optical coherence tomography of idiopathic polypoidal choroidal vasculopathy. Am J Ophthalmol 127:301-305.
24. Iijima H, Iida T, Imai M, Tsukahara S (2000) Optical coherence tomography of orange-red subretinal lesions in eyes with idiopathic polypoidal choroidal vasculopathy. Am J Ophthalmol 129:21-26.
25. Sato T, Kishi S, Watanabe G, Matsumoto H, Mukai R (2007) Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. Retina 27:589-594.
26. Kameda T, Tsujikawa A, Otani A, Sasahara M, Gotoh N, Tamura H, Yoshimura N (2007) Polypoidal choroidal vasculopathy examined with en face optical coherence tomography. Clin Experiment Ophthalmol 35:596-601.
27. Kon Y, Iida T, Maruko I, Saito M (2008) The optical coherence tomography-ophthalmoscope for examination of central serous chorioretinopathy

with precipitates. Retina 28:864-869.

28. Tsujikawa A, Sasahara M, Otani A, Gotoh N, Kameda T, Iwama D, Yodoi Y, Tamura H, Mandai M, Yoshimura N (2007) Pigment epithelial detachment in polypoidal choroidal vasculopathy. Am J Ophthalmol 143:102-111.

29. Ojima Y, Hangai M, Sakamoto A, Tsujikawa A, Otani A, Tamura H, Yoshimura N (2009) Improved visualization of polypoidal choroidal vasculopathy lesions using spectral-domain optical coherence tomography. Retina 29:52-59.

30. Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK, Iliev ME, Frey M, Rothenbuehler SP, Enzmann V, Wolf S (2009) Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. Invest Ophthalmol Vis Sci 50:3432-3437.

31. Yamada E (1969) Some structural features of the fovea centralis in the human retina. Arch Ophthalmol 82:151-159.

32. Matsumoto H, Sato T, Kishi S (2009) Outer nuclear layer thickness at the fovea determines visual outcomes in resolved central serous chorioretinopathy. Am J Ophthalmol. 148:105-110.

33. Marmor MF (1999) Mechanisms of fluid accumulation in retinal edema. Doc Ophthalmol 97:239-249.

Figure Legends

Figure 1. Spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise of a normal eye (eye of a 60-y-old man whose best-corrected visual acuity was 1.5 with -1.5 diopters of myopia). **A**, Horizontal scan through the fovea centralis obtained at a 30^{o} angle width. **B**, Magnified view. SD-OCT with reduced speckle noise showed 4 highly reflective lines in this normal eye, namely, the external limiting membrane (ELM), the junction between the photoreceptor inner and outer segments (IS/OS), an intermediate reflective line between the IS/OS line and retinal pigment epithelium (RPE), and the RPE. Thickness of the outer nuclear layer (ONL), which is the distance between the outer border of the inner limiting membrane and the ELM, is 131 μm. Thickness of the inner segment (IS), which is the distance between the ELM and the inner border of the IS/OS, is 30 μm. Thickness of the outer segment (OS), which is the distance between the inner borders of the IS/OS and RPE, is 62 μm.

Figure 2. Ophthalmologic examination of the eye of a 57-y-old man with central serous chorioretinopathy (CSC) and a 1-mo history of decreased visual acuity (VA) in the right eye; his VA was 0.7.

At the baseline. **A**, Funduscopic examination shows subretinal fluid. **B**–**E**, Early-phase (**B**) and mid-phase (**D**) fluorescein angiography (FA) shows intense leakage in an inkblot pattern. Early-phase (**C**) and mid-phase (**E**) indocyanine green angiography (IA) do not show polypoid lesions. Hyperfluorescent area corresponds to a leaking point seen using FA. **F**, Vertical scan through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in C. Spectral-domain optical coherence tomography (SD-OCT) image shows serous retinal detachment. **G**, Magnified view of F. Thickness of the outer nuclear layer (ONL) is 88 μm, that of the

inner segment (IS) is 22 μm, and that of the outer segment (OS) is 56 μm.
After 2 mo, the retina attached spontaneously.
At last follow-up (after 12 mo), the man's VA was 1.5. **H**, Vertical scan through the fovea centralis obtained at a 30° angle width. Resolved serous retinal detachment. **I**, Magnified view of H. Thickness of the ONL is 88 μm, that of the IS is 22 μm, and that of the OS is 46 μm.

Figure 3. Ophthalmologic examination of the eye of a 71-y-old man with polypoidal choroidal vasculopathy (PCV) and a 2-mo history of decreased visual acuity (VA) in right eye; his VA was 0.2.
At the baseline. **A**, Funduscopic examination shows subretinal hemorrhage, subretinal fluid, and reddish-orange nodules. **B** and **C**, Simultaneously obtained fluorescein angiography (FA) (**B**) and indocyanine green angiography (IA) (**C**) images. IA shows a small branching vascular network that terminates in polypoid lesions. **D**, Horizontal scan through the fovea centralis obtained at a 30° angle width, corresponding to the arrow indicated in C. Spectral-domain optical coherence tomography (SD-OCT) image shows serous retinal detachment and polypoid lesions. **E**, Magnified view of D. Thickness of the outer nuclear layer (ONL) is 70 μm, that of the inner segment (IS) is 15 μm, and that of the outer segment (OS) is 22 μm.
Photodynamic therapy combined with intravitreal triamcinolone acetonide and bevacizumab was given to the patient. After 2 mo, serous retinal detachment resolved. At last follow-up (after 6 mo), the patient's VA was 0.2. **F**, Horizontal scan through the fovea centralis obtained at a 30° angle width shows that the serous retinal detachment has resolved. **G**, Magnified view of F. Thickness of the ONL is 62 μm, that of the IS is 14 μm, and that of the OS is 11 μm.

Figure 4. Comparison of the inner segments (IS) and outer segments (OS) in eyes with central serous chorioretinopathy (CSC) and polypoidal choroidal vasculopathy (PCV).

A, Ophthalmologic examination of the eye of a 37-y-old man with CSC and 1-mo history of visual disturbance; his visual acuity (VA) was 1.0. (Left) Funduscopic examination shows serous retinal detachment. (Right) Mid-phase fluorescein angiography shows leakage in a smokestack pattern. **B**, Horizontal line scan through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in **A**. Image obtained using spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise shows elongation of the OS.

C, Ophthalmologic examination of the eye of a 64-y-old man with PCV and 1-mo history of visual disturbance; his VA was 0.8. (Left) Funduscopic examination shows serous retinal detachment, pigment epithelial detachment, and reddish-orange nodules. However, fibrin or hemorrhage are not seen in the subretinal space. (Right) Indocyanine green angiography (IA) shows a small branching vascular network that terminates in polypoid lesions. The hypofluorescent area corresponds to serous retinal detachment. **D**, Vertical line scan of SD-OCT with reduced speckle noise through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in **C**. Thickness of IS and OS are relatively unchanged.

E, Ophthalmologic examination of the eye of a 60-y-old woman with PCV and 2-mo history of visual disturbance; her VA was 0.2. (Left) Funduscopic examination shows serous retinal detachment, reddish-orange nodules, fibrin, and hemorrhage in the subretinal space (arrow). (Right) IA shows a small branching vascular network that terminates in polypoid lesions. **F**, Vertical line scan through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in **D**. High reflectivity area suggesting fibrin or hemorrhage is observed in the subretinal space

(arrow). SD-OCT with reduced speckle noise shows the thinning of the IS and OS.

ELM = external limiting membrane

Table

Table 1. Patient Characteristics and Fundus Findings

	CSC (n = 36)	PCV (n = 23)	*P* value
Men/Women (n)	31/5	17/6	0.245*
Age (y) mean +/- 1 SD	49.0 ± 11.3 (37~73)	71.3 ± 8.2 (57~92)	<0.001†
Follow-up period (mo) mean +/- 1 SD	7.1 ± 3.4 (3~15)	9.0 ± 4.1 (3~16)	<0.001†
Median duration of symptoms	3.0 mo (2 wk~4 y)	3.0 mo (1 mo~6 y)	
Mean height of SRD at fovea (μm) mean +/- 1 SD	191 ± 107	185 ± 111	0.971†
Mean distance from fovea to nearest point of attachment to the retina (μm) mean +/- 1 SD	1427 ± 542	1710 ± 573	0.090†
Fibrin	7/36 (19%)	13/23 (57%)	0.001*
Subretinal hemorrhage	0/36 (0%)	15/23 (65%)	<0.001*
Mean logMAR at baseline	0.13	0.36	0.006†
Resolution of SRD at last follow-up	23/36 (64%)	15/23 (65%)	0.918*
Mean logMAR at last follow-up	0.06	0.28	0.007†

*Fisher's exact test, †Tukey-Kramer test.

CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, SRD = serous retinal detachment, SD=standard deviation, log MAR=logarithm of minimal angle of resolution

y=year, mo=month, and wk=week

Table 2. Inter-observer Reproducibility of the Measurement of Retinal Thickness Using SD-OCT with Reduced Speckle Noise: Intraclass Correlation Coefficient

	Normal (n = 44)	CSC (n = 36)	PCV (n = 23)
ONL	0.972	0.969	0.963
IS	0.970	0.964	0.961
OS	0.975	0.958	0.953

SD-OCT = spectral-domain optical coherence tomography, CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, ONL = outer nuclear layer, IS = inner segment, and OS = outer segment.

Table 3. Retinal Thickness at the Baseline and at Last Follow-up

		Retinal thickness (μm)					
		Normal (n = 44)	**CSC (n = 36)**	***P* value***	**PCV (n = 23)**	***P* value†**	***P* value**
ONL	baseline mean +/- 1 SD	126 ± 23 (88~187)	88 ± 21 (52~136)	<0.001	89 ± 26 (32~140)	<0.001	0.998‡
	last follow-up mean +/- 1 SD		84 ± 22 (39~136)		87 ± 28 (30~139)		0.747§
IS	baseline mean +/- 1 SD	30 ± 5 (21~38)	21 ± 4 (8~28)	<0.001	18 ± 6 (8~29)	<0.001	0.034‡
	last follow-up mean +/- 1 SD		20 ± 4 (8~26)		17 ± 5 (6~29)		0.018§
OS	baseline mean +/- 1 SD	56 ± 6 (40~68)	62 ± 28 (14~137)	0.394	33 ± 16 (14~68)	<0.001	<0.001‡
	last follow-up		54 ± 36 (11~134)		30 ± 14 (6~58)		0.004§

	mean +/- 1 SD

*Tukey-Kramer test, *P* value of normal eyes and eyes with CSC.

†Tukey-Kramer test, *P* value of normal eyes and eyes with PCV.

‡Tukey-Kramer test, *P* value of eyes with CSC and PCV.

§Unpaired *t*-test, *P* value of eyes with CSC and PCV.

CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, ONL = outer nuclear layer, IS = inner segment, OS = outer segment, and SD=standard deviation

Table 4. Comparison of Retinal Thickness and Visual Acuity between Eyes with PCV, with or without the Presence of Subretinal Fibrin or Hemorrhage.

	Fibrin or Hemorrhage (-) (n = 8)	**Fibrin or Hemorrhage (+) (n = 15)**	***P* value***
ONL (μm) mean +/- 1 SD	90 ± 32	88 ± 23	0.872
IS (μm) mean +/- 1 SD	22 ± 5	15 ± 4	0.001
OS (μm) mean +/- 1 SD	43 ± 19	27 ± 12	0.022
logMAR	0.136	0.477	0.035

*Unpaired *t*-test

PCV = polypoidal choroidal vasculopathy, SRH = subretinal hemorrhage, ONL = outer nuclear layer, IS = inner segment, and OS = outer segment, and SD=standard deviation, log MAR=logarithm of minimal angle of resolution

Supplemental Table 1. Retinal Thickness at the Baseline and at Last Follow-up in Subjects over 60 Years Old without Fibrin or Hemorrhage in the Subretinal Space

		Retinal thickness (μm)					
		Normal (n = 42)	**CSC (n = 6)**	***P* value***	**PCV (n = 6)**	***P* value†**	***P* value**
ONL	baseline mean +/- 1 SD	126 ± 23	82± 17	<0.001	86 ± 20	<0.001	0.966‡
	last follow-up mean +/- 1 SD		82 ± 11		87 ± 20		0.539§
IS	baseline mean +/- 1 SD	30 ± 5	22 ± 3	0.004	20 ± 6	<0.001	0.637‡
	last follow-up mean +/- 1 SD		21 ± 3		18 ± 4		0.066§
OS	baseline mean +/- 1 SD	56 ± 6	73 ± 33	0.016	37 ± 20	0.003	<0.001‡
	last follow-up mean +/- 1 SD		46 ± 16		26 ± 9		0.025§

*Tukey-Kramer test, *P* value of normal eyes and eyes with CSC.

†Tukey-Kramer test, *P* value of normal eyes and eyes with PCV.

‡Tukey-Kramer test, *P* value of eyes with CSC and PCV.

§Unpaired *t*-test, *P* value of eyes with CSC and PCV.

CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, ONL = outer nuclear layer, IS = inner segment, OS = outer segment, SD=standard deviation

Figure 1

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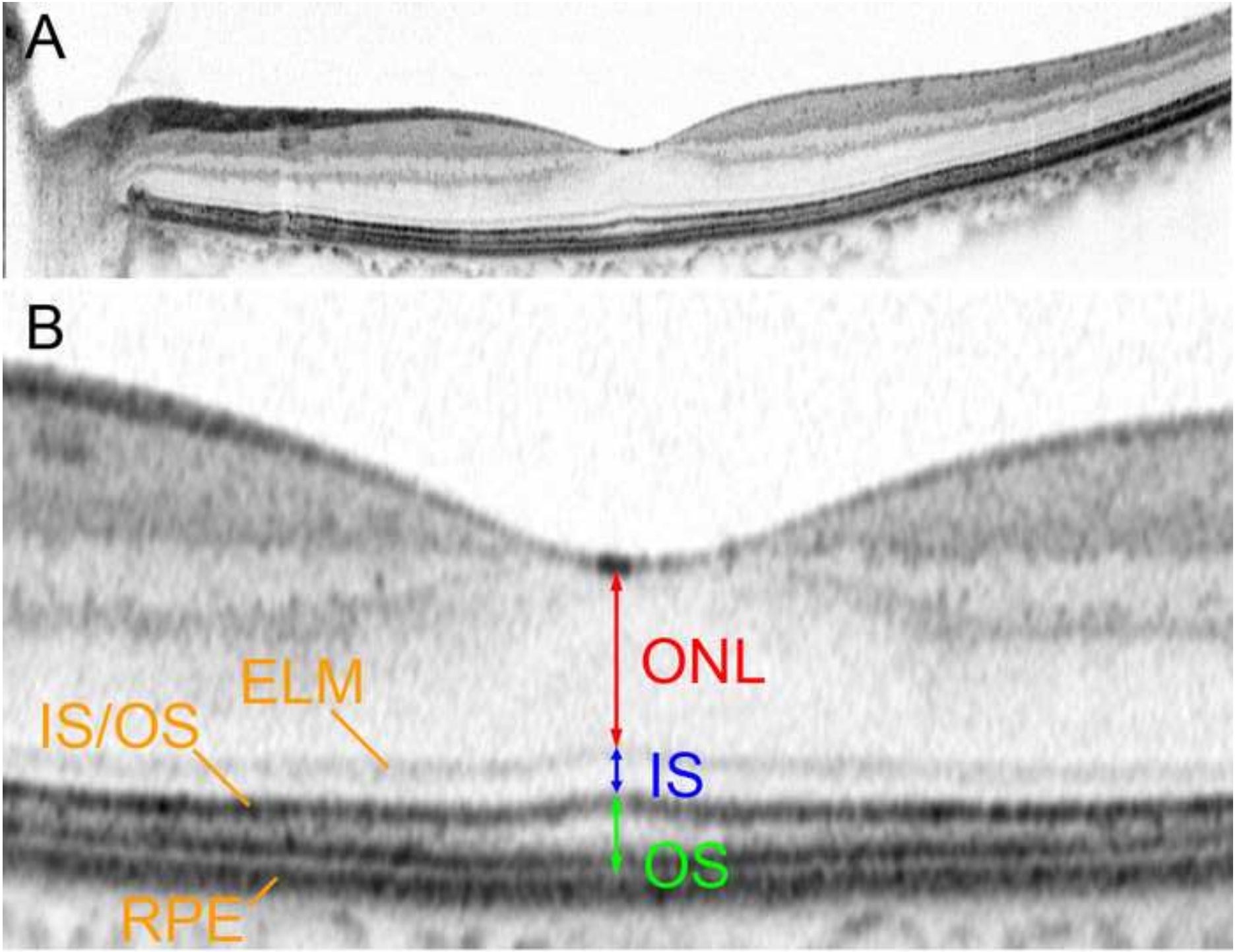

Figure 2A-E

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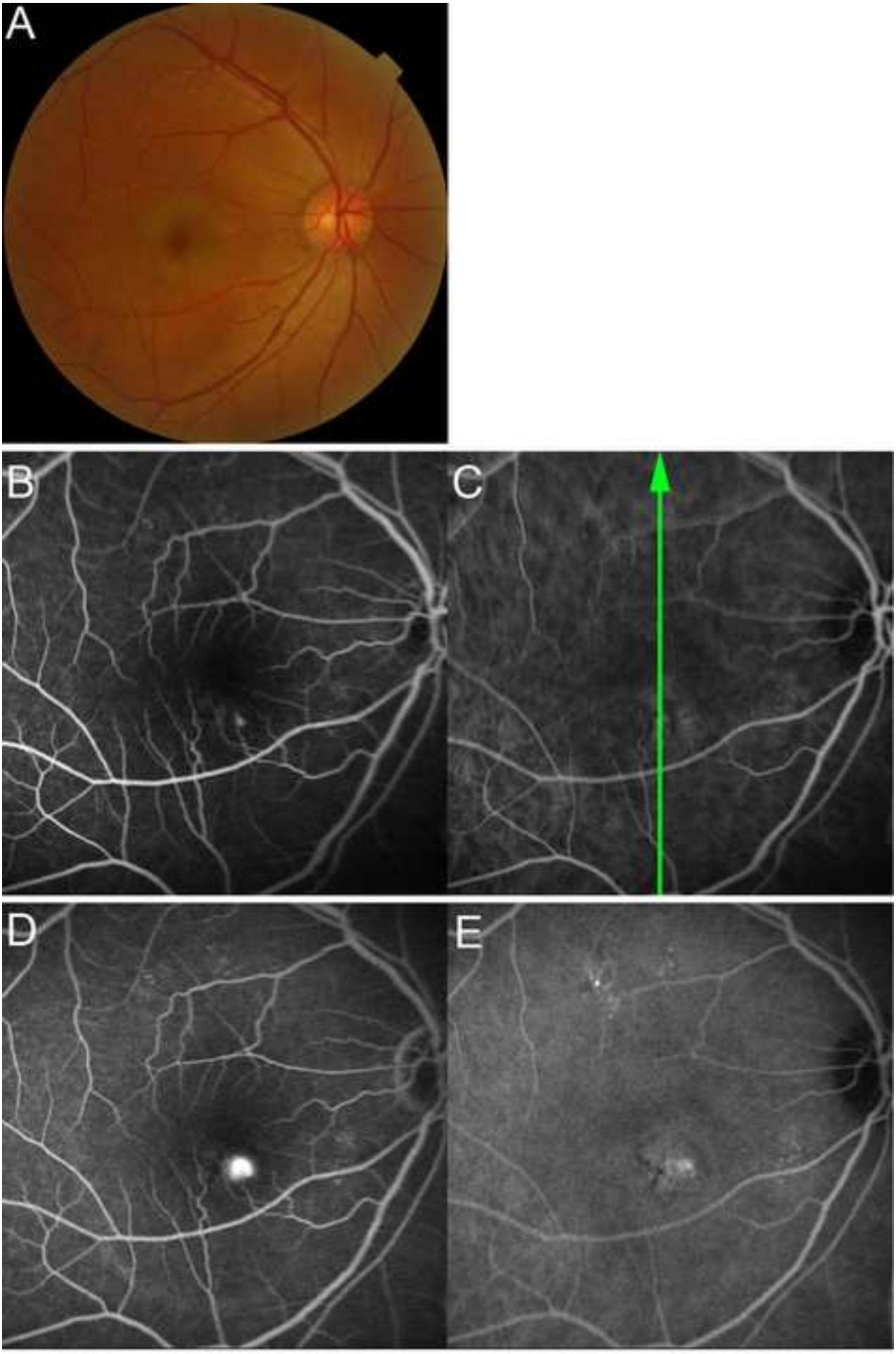

Figure 2F-I

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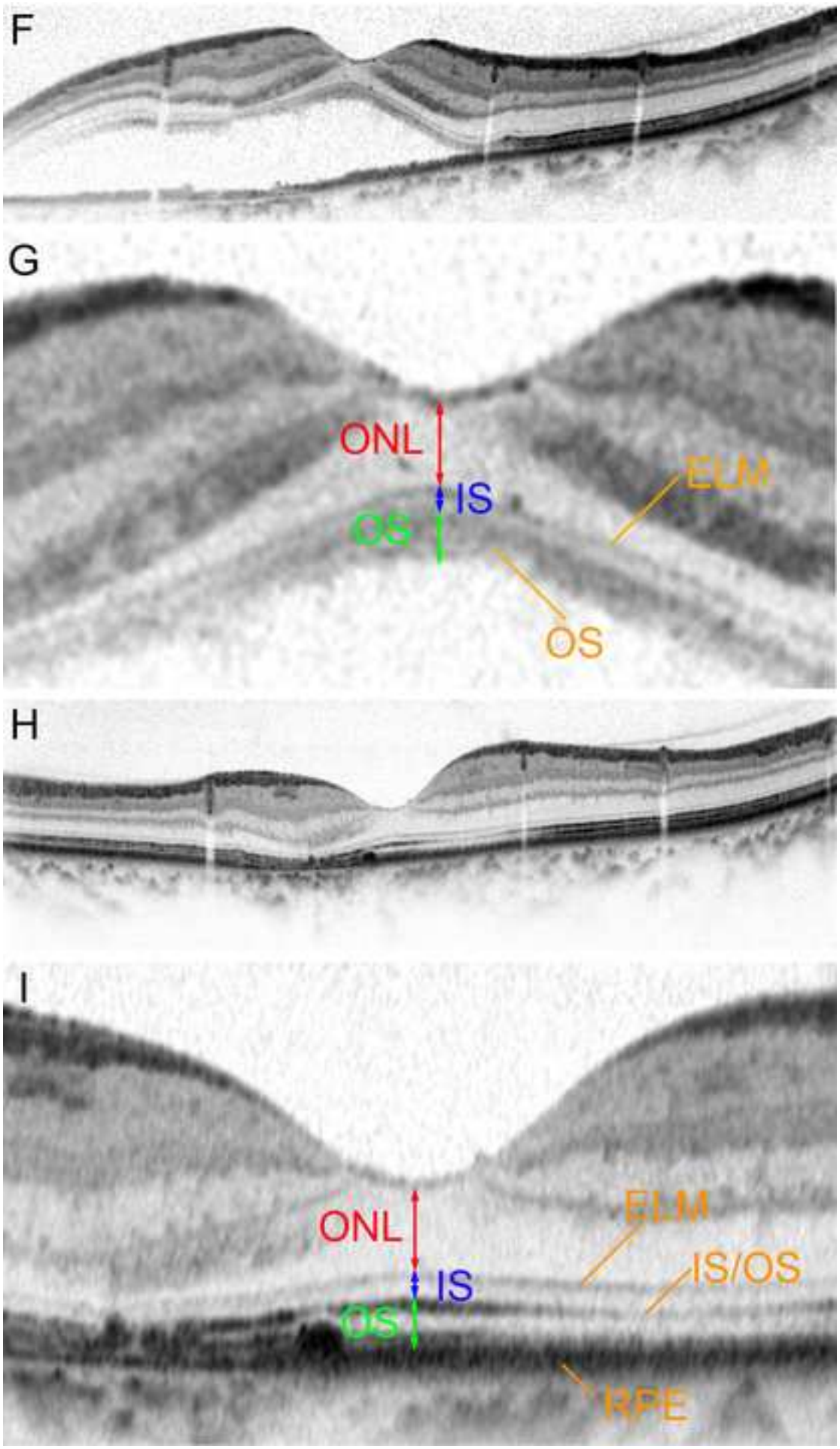

Figure 3A-D

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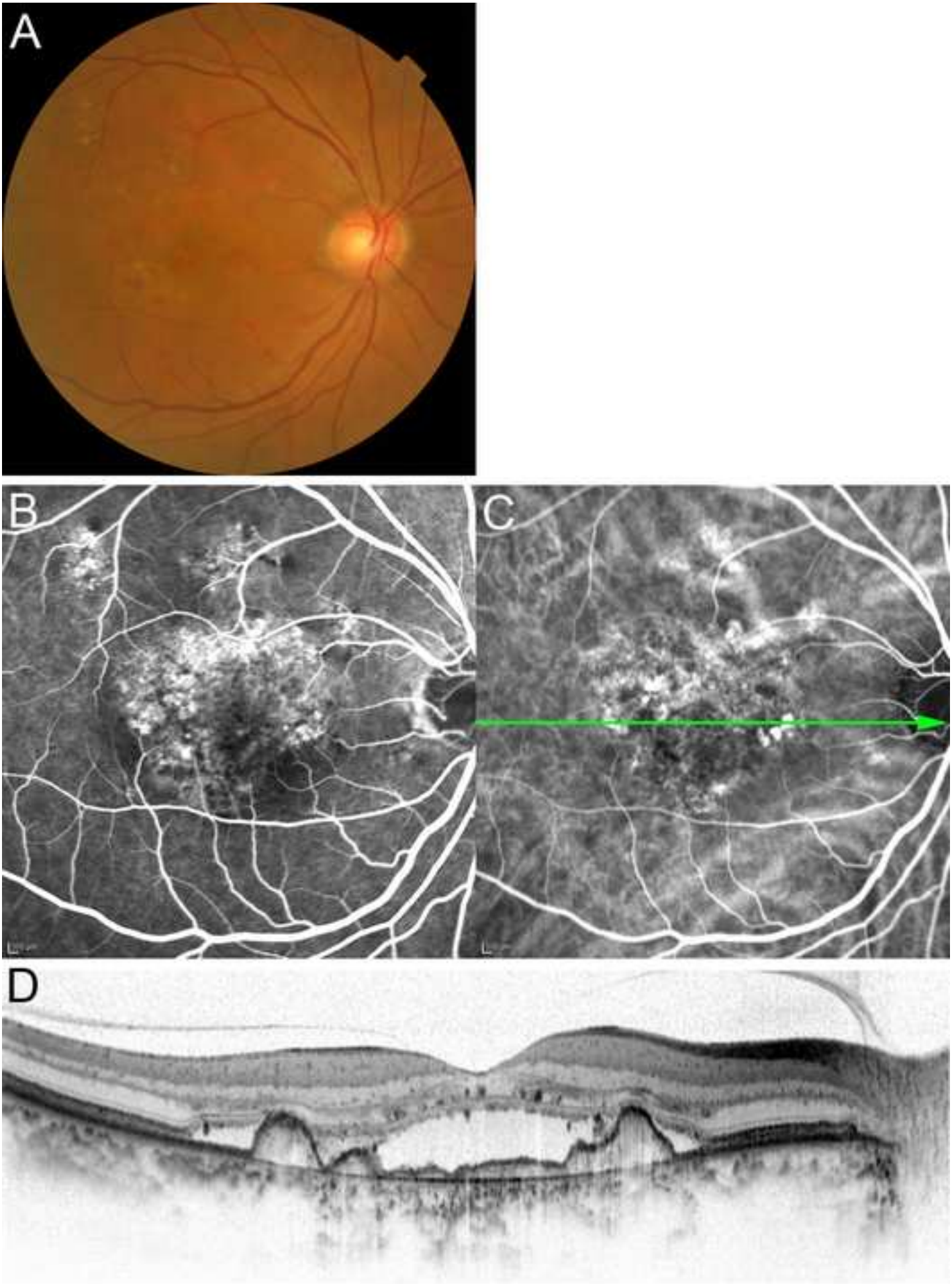

Figure 3E-G

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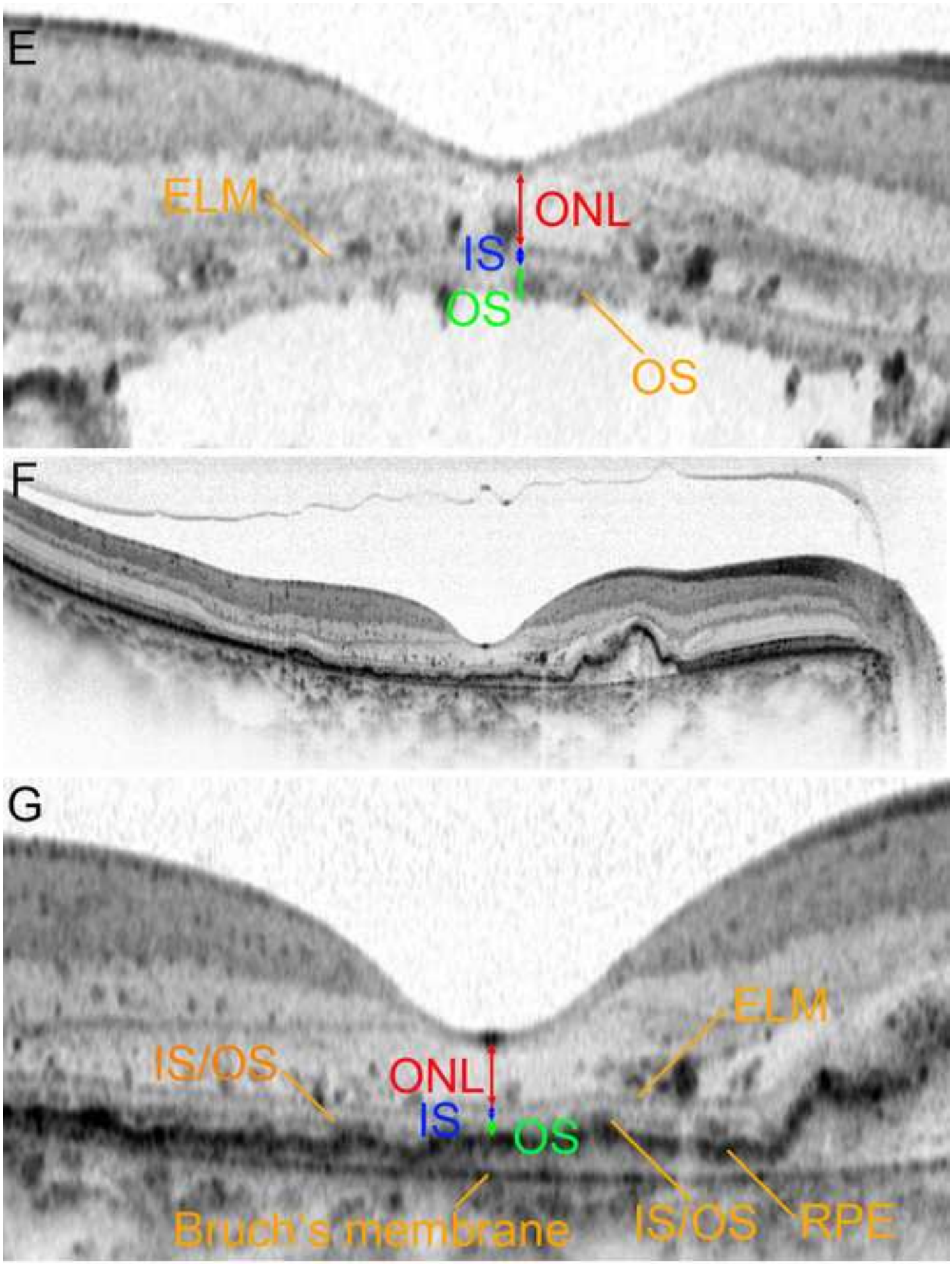

Figure 4A-C

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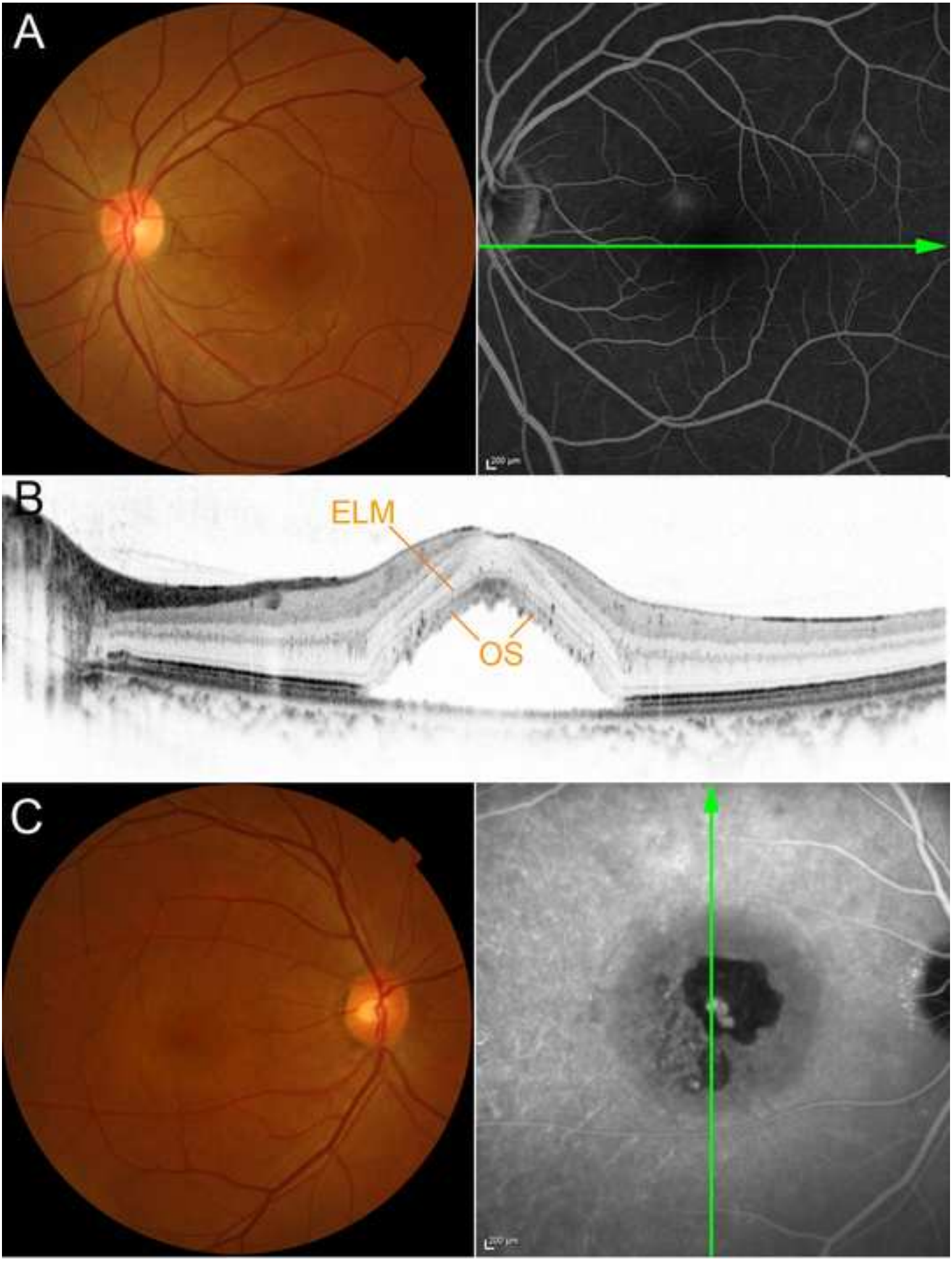

Figure 4D-F

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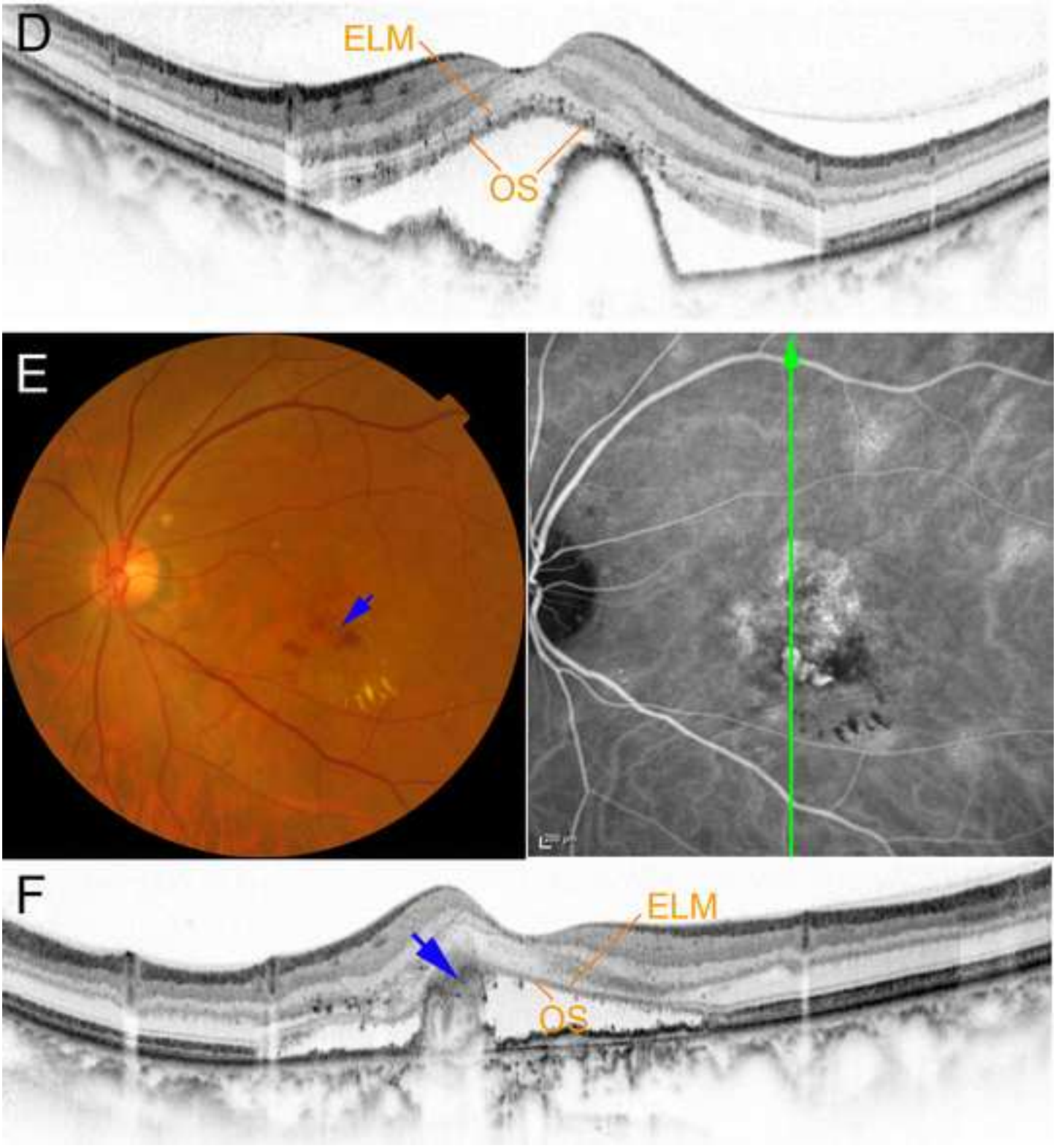

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I, Sotaro Ooto hereby confirm that all named authors meet the ICMJE

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requirement of authorship and meet all three criteria as mentioned below:

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~~Thinning~~ Thickness of photoreceptor layers in polypoidal choroidal vasculopathy and central serous chorioretinopathy

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This article contains a Table as additional online-only material. The following should appear online-only: Supplemental Table 1.

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Abstract

Background: To evaluate retinal thickness using spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise in eyes with polypoidal choroidal vasculopathy (PCV) compared to those with normal eyes and central serous chorioretinopathy (CSC).

Methods: We retrospectively reviewed cases of foveal serous retinal detachment in 36 eyes of 36 patients with active CSC and 23 eyes of 23 patients with active PCV, and 44 eyes of 44 normal subjects. Patients were examined using SD-OCT with reduced speckle noise, and the thickness of the outer nuclear layer (ONL), photoreceptor inner segment (IS), and photoreceptor outer segment (OS) were measured.

Results: The ONL and IS wereas thicker in normal eyes than in eyes with CSC or PCV ($P < 0.001$); it was also thicker in eyes with CSC than in eyes with PCV ($P = 0.034$). The OS was significantly less thick in eyes with PCV than in normal eyes ($P < 0.001$), whereas there was no significant difference between eyes with CSC and normal eyes. The thickness of IS and OS in eyes with PCV was related to fibrin or hemorrhage being present in the subretinal space. In eyes with PCV, best-corrected visual acuity at baseline correlated with IS thickness ($P = 0.023$).

Conclusions: Thinning of each photoreceptor layer was observed in the eyes of PCV patients as compared to that observed in the case of normal individuals. The differentiating factors between PCV and CSC, observed using SD-OCT, include the thinning of the IS and OS in eyes with PCV, which makes SD-OCT helpful in differentiating PCV from CSC. More severe photoreceptor alterations were seen in PCV because fibrin and hemorrhage were present in the subretinal space, which correlated with poorer vision.

Keywords Central serous chorioretinopathy, Optical coherence tomography, Polypoidal choroidal vasculopathy, Photoreceptor inner segment, Photoreceptor outer segment

Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by multiple terminal reddish-orange nodules and a complex network of vessels in the eye, and often causes serous retinal detachment (SRD) or pigment epithelial detachments (PEDs)[1-6]. While its pathogenesis is not yet fully understood, PCV originates in an abnormality of the inner choroidal vessels and is presumed to be a variant of choroidal neovascularization (CNV).

Central serous chorioretinopathy (CSC) is characterized by SRD in the macular area, often in association with small serous PEDs and retinal pigment epithelial atrophy [7, 8]. Evaluation using indocyanine green angiography (IA) shows multifocal staining islands in the inner choroid, suggesting that exudative changes within the inner choroid constitute the primary event in CSC [9-14].

Some cases of PCV have clinical, fluorescein angiography (FA), IA, or tomographic findings similar to those of CSC, and it is difficult to differentiate these cases from those of CSC [3-5]. Choroidal vascular hyperpermeability, a characteristic finding in CSC, might be involved in the pathogenesis of PCV, suggesting that the pathogenesis of PCV and CSC is similar in part [4]. Further, both PCV and CSC are associated with SRD. However, most CSC patients have good visual acuity (VA) despite macular detachment, whereas many PCV patients have decreased VA. The changes in retinal morphology that lead to these different visual outcomes have not been documented.

Optical coherence tomography (OCT) is the primary technique for studying both PCV and CSC. OCT has recently evolved into spectral-domain OCT (SD-OCT), which has 43–100 times higher imaging speeds than time-domain OCT (TD-OCT) as well as a much higher signal-to-noise ratio [15-17]. A new SD-OCT instrument, the Spectralis™ HRA+OCT (Heidelberg Engineering, Dossenheim, Germany), combines confocal

scanning laser ophthalmoscopy and SD-OCT. It also allows the integration of information obtained from FA, IA, and SD-OCT, thus enabling the determination of the exact site of origin of a disease. Additionally, this new instrument uses an eye-tracking system to eliminate motion artifacts, which limit the detection of small changes in the eye. Combining eye tracking with multiple B-scan averaging [18] permits the production of finely detailed images of all retinal layers with reduced speckle noise. These technological advances enable more accurate measurements of each retinal layer, and should help to differentiate between the pathologic features of CSC and PCV.

In this study, we used the SD-OCT system with reduced speckle noise to examine the retinal structure in eyes with PCV and foveal SRD as compared to normal eyes or eyes with CSC and foveal SRD. We also studied the changes in fine structural factors, such as the thickness of the outer nuclear layer (ONL), photoreceptor inner segment (IS), and photoreceptor outer segment (OS), to determine the association between structural changes and visual function.

Subjects and Methods

For this observational case study, we retrospectively reviewed 44 eyes of 44 normal subjects (36 men and 8 women) as controls, 36 eyes of 36 patients with active CSC (31 men and 5 women) and 23 eyes of 23 patients with active PCV (17 men and 6 women) (Table 1). We enrolled PCV and CSC patients who visited the Macular Service in Kyoto University Hospital, Kyoto, Japan, for the first time between November 2007 and March 2009. All patients were Japanese. The mean age of normal subjects was 68.2 (range, 49–84 years); that of CSC patients, 49.0 (range, 37–73 years) (compared to normal subjects, $P < 0.001$, Tukey-Kramer test); and that of PCV patients, 71.3 (range, 57–92 years) (compared to normal subjects, $P = 0.345$, Tukey-Kramer test). The duration of symptoms ranged from 2 weeks to 4 years (median, 3.0 months) for CSC

and from 1 month to 6 years (median, 3.0 months) for PCV. Eight eyes had recurrent CSC and 6, chronic CSC (defined as SRD wherein the duration of symptoms was more than 6 months). Only eyes with active CSC or active PCV that had foveal SRD were included. Eyes with a history of photocoagulation, photodynamic therapy, or vitreous surgery were excluded. All investigations adhered to the tenets of the Declaration of Helsinki, and the current study was approved by the institutional review board and the ethics committee at Kyoto University Graduate School of Medicine.

All patients underwent a comprehensive ophthalmologic examination, including assessment of best-corrected VA (BCVA) and intraocular pressure, and assessment using indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, fundus photography, and simultaneous FA and IA with a confocal laser scanning system (Spectralis™ HRA+OCT).

The diagnosis of CSC or PCV was based on fundus photograph, FA, and IA. In eyes with PCV, IA shows a branching vascular network terminating in either a single polyp or a cluster of multiple polyps. In most cases, reddish-orange nodules observed by ophthalmoscopic examination correspond to the polypoidal lesion seen by IA. In eyes with CSC, FA shows leakage from the RPE, and IA shows an absence of polypoidal choroidal vascular lesions. 2 macular experts (NY and AT) examined all the acquired color fundus photographs, FA, and IA. They worked independently. When their evaluations did not agree, the opinion of a third observer (SO) was invited and the results were discussed until consensus was reached.

Retinal imaging was performed using the Spectralis™ HRA+OCT. First, horizontal and vertical line scans through the fovea centralis were obtained at a 30^{o} angle, followed by 12 radial scans (6 mm) centered at the fovea; finally, 19 serial horizontal scans (6 mm) were obtained. At each location of interest on the retina, 12~50 SD-OCT images were acquired and averaged to reduce speckle noise.

Using these SD-OCT images, we analyzed the morphologic changes in the retina in eyes with CSC or PCV. To measure the thickness of the intraretinal structures in normal eyes and eyes with CSC or PCV, we chose 3~5 B-scan images with the deep foveal depression from the vertical, horizontal, and radial scans of the fovea. These B-scan images were sent to the Kyoto University OCT Reading Center at the Kyoto University Graduate School of Medicine (Kyoto, Japan). By using the digital caliper tool built into the SD-OCT system with reduced speckle noise, retinal thickness was then measured by 2 independent experienced observers (MY and AH) who were unaware of the diagnosis or other clinical information regarding the eyes. The thickness of each retinal layer was the mean thickness determined using these B-scan images.

At the fovea, we measured the thickness of the ONL, which is approximately the distance between the outer border of the internal limiting membrane (ILM) and external limiting membrane (ELM); IS, which is approximately the distance between the ELM and the inner border of the junction between the IS and OS (IS/OS); and OS. In an attached retina, the thickness of the OS is approximately the distance between the inner borders of the IS/OS and retinal pigmented epithelium (RPE). In a detached retina, the thickness of the OS is approximately the distance between the inner border of the IS/OS and the tip of the OS.

Patients underwent BCVA and fundus assessment and SD-OCT examination at every visit. Intravitreal bevacizumab or photodynamic therapy combined with intravitreal triamcinolone acetonide and intravitreal bevacizumab was given to 11 and 5 eyes with PCV, respectively, and photocoagulation or photodynamic therapy was performed in 3 and 5 eyes with CSC, respectively, during the follow-up period.

BCVA measured using the Landolt Chart was expressed as the logarithm of minimal angle of resolution (logMAR) for statistical calculation. For comparing the

patient characteristic variables, Tukey-Kramer test~~an unpaired *t*-test~~ and Fisher's exact test were used. ~~For inter-observer measurements, t~~The ~~coefficients of variation~~intraclass correlation coefficient (ICC~~CV~~) was~~ere~~ obtained ~~from the variance component between the individuals~~as inter-observer reproducibility measure. For comparing the differences in retinal thickness between normal eyes and eyes with CSC or PCV, Tukey-Kramer test was used. For comparing the differences in retinal thickness between eyes with fibrin or subretinal hemorrhage and those without it, an unpaired *t*-test was used. We used the Spearman rank correlation coefficient to study the association between BCVA and the thickness of the ONL, IS, or OS. All statistical evaluations were performed using a commercially available software program (SPSS17; SPSS Inc., Chicago, IL). *P* less than 0.05 was considered statistically significant.

Results

For this study, we selected eyes with foveal SRD and CSC or PCV. The height or area of SRD did not significantly differ between eyes with CSC and PCV (*P* = 0.~~859~~ 971 for height and 0.~~121~~ 090 for area, Tukey-Kramer test~~unpaired *t*-test~~). Fibrin was observed in the subretinal space in 7 of the 36 eyes with CSC (19%) and 13 of the 23 eyes (57%) with PCV (*P* = 0.001, Fisher's exact test). Subretinal hemorrhage was not seen in any eye with CSC, but it was observed in 15 eyes with PCV (65%; *P* < 0.001, Fisher's exact test). At last follow-up, foveal SRD resolved in 23 eyes with CSC (64%) and 15 eyes with PCV (65%) (*P* = 0.918, Fisher's exact test) (Table 1).

The mean BCVA at the baseline was 0.75 (range, 0.06–1.5; 0.13 logMAR) for eyes with CSC and 0.44 (range, 0.02–1.5; 0.36 logMAR) for eyes with PCV. Thus, at the baseline, eyes with CSC had better BCVA than those with PCV (*P* = 0.0062~~4~~, Tukey-Kramer test~~unpaired *t*-test~~). The mean BCVA at last follow-up was 0.87 (range,

0.06–1.5; 0.06 logMAR) for eyes with CSC and 0.52 (0.28 logMAR; range, 0.04–1.5) for eyes with PCV; therefore, eyes with CSC had better BCVA than eyes with PCV at the last follow-up as well (*P* = 0.~~032~~007,~~-~~Tukey-Kramer test~~unpaired *t*-test~~).

The images obtained using SD-OCT with reduced speckle noise showed 4 highly reflective lines in each normal eye, namely the ELM, the IS/OS, an intermediate reflective line between IS/OS and RPE, and the RPE (Fig 1). In each eye with CSC or PCV, the detached retina showed the ELM, and the IS/OS lines, but not the intermediate reflective line (Figs 2–4).

Inter-observer reproducibility of the measurement of retinal thickness by using SD-OCT with reduced speckle noise was assessed by calculating inter-observer ~~CVs~~ICC; ~~CVs~~ ICC ranged from 0.953-0.975~~1.09–4.05%~~ for the measurement of ~~thickness of~~ each retinal layer thickness(Table 2).

At the central fovea, the mean ONL thickness was significantly lower in eyes with CSC or PCV than in normal eyes (*P* < 0.001, Tukey-Kramer test) (Table 3). In contrast, the mean ONL thickness did not differ between eyes with CSC and PCV (*P* = 0.998, unpaired *t*-test), and this was also observed at the last follow-up (*P* = 0.747, unpaired *t*-test).

At the initial examination, the mean IS thickness was significantly lower in eyes with CSC or PCV than in normal eyes (*P* < 0.001, Tukey-Kramer test) (Table 3). Moreover, the IS thickness was significantly lower in eyes with PCV than in those with CSC (*P* = 0.034, Tukey-Kramer test). The IS thickness at the last follow-up was significantly lower in eyes with PCV than in those with CSC (*P* = 0.018, unpaired *t*-test).

At the central fovea, the mean OS thickness was significantly lower in eyes with PCV than in normal eyes (*P* < 0.001, Tukey-Kramer test), whereas there was no significant difference between the OS thickness in eyes with CSC and normal eyes (*P* = 0.394, Tukey-Kramer test) (Table 3). The elongation of the OS (>60 μm) was observed

in 17 of the 36 eyes with CSC (47%). In contrast, this elongated OS was observed only in 2 of the 23 eyes with PCV (9%; $P = 0.002$, Fisher's exact test). At the last follow-up, the mean OS thickness was significantly lower in eyes with PCV than in those with CSC ($P = 0.004$, unpaired *t*-test).

The thickness of IS and OS in eyes with PCV was related to the presence of fibrin or hemorrhage in the subretinal space (Table 4, Fig. 4). The thickness of IS and OS in eyes with fibrin or hemorrhage was significantly lower than that in eyes without fibrin or hemorrhage ($P = 0.001$ and 0.022, respectively, unpaired *t*-test). Moreover, BCVA was significantly worse in eyes with fibrin or hemorrhage than in eyes without it ($P = 0.035$, unpaired *t*-test). The ONL thickness was not related to fibrin or hemorrhage.

~~The thickness of the ONL, IS, and OS in each group was examined only in individuals over 60 years of age, and the results thus obtained were similar (Supplemental Table 1). The mean ±SD age (in years) of these subgroups did not differ significantly (68 ± 6 for normal eyes, 67 ± 9 in eyes with CSC, and 72 ± 8 in eyes with PCV).~~

The thickness of the ONL, IS, and OS layers in each group was examined only in individuals who were more than 60 years old and did not exhibit fibrin or hemorrhage in the subretinal space (Supplemental Table 1). On comparison with the normal individuals, the CSC and PCV patients exhibited thinning of the ONL and IS layers; however, the difference in the thickness of the IS layer between the CSC and PCV patients was not significant. Compared with the normal individuals, the CSC patients exhibited a significant increase and the PCV patients exhibited a significant decrease in the thickness of the OS layer. The mean ± SD age (in years) of the individuals in these subgroups did not significantly differ (normal individuals, 68 ± 6; CSC patients, 67 ± 9; and PCV patients, 72 ± 8). In addition, the mean follow-up period, mean distance from the fovea to the nearest point of attachment to the retina, and mean baseline logMAR

score did not significantly differ among the subgroups (P = 0.414, 0.244, and 0.359, respectively; Tukey-Kramer test).

In eyes with CSC, the logMAR BCVA at the baseline correlated with ONL thickness (P = 0.003, $r\!R^2$ = 0.23) and IS thickness (P = 0.022, $r\!R^2$ = 0.14), although there was no correlation between logMAR BCVA and OS, and this was the case even at the last follow-up (P = 0.002 for ONL thickness and P < 0.001 for IS thickness).

In eyes with PCV, the logMAR BCVA at the baseline correlated with IS thickness (P = 0.023, $r\!R^2$ = 0.22); it weakly correlated or did not correlate with OS thickness (P = 0.075). At the last follow-up, logMAR BCVA correlated with IS thickness (P = 0.001, $r\!R^2$ = 0.44) and OS thickness (P = 0.033, $r\!R^2$ = 0.38).

Discussion

OCT has provided a better understanding of the mechanisms underlying the development of both CSC and PCV [19-29]. The use of TD-OCT showed increased thickening and granularity of the outer photoreceptor layer in the SRD area in eyes with CSC [19, 20]. Using SD-OCT, Matsumoto et al showed that the OS was elongated and that ONL thickness was decreased in eyes with CSC [21]. Ojima et al found that a large defect in the inner and outer segments of foveal photoreceptors correlated with poor VA [22]. OCT imaging of eyes with PCV revealed sharp protrusions of the RPE with moderate inner reflectivity; the protrusions were associated with reddish-orange nodules seen on fundus photography [23, 24]. In eyes with PCV, a double-layered line at the RPE level was found to be associated with a branching vascular network [25]. To date, however, limited information is available on the retinal structures in eyes with PCV, and the different morphological changes in the retina in CSC or PCV have not been documented in detail.

The clinical utility of any instrument depends on the reproducibility of the measurements obtained with it. A new SD-OCT with reduced speckle noise, the Spectralis™ HRA+OCT, eliminates motion artifacts, which limit the detection of small changes in the eye, using an eye-tracking system. These technological advances enable more accurate and reproducible measurement of each retinal layer. In fact, Wolf-Schnurrbusch et al reported that Spectralis™ HRA+OCT had the best measurement repeatability among 6 different OCT instruments [30]. In the current study, the inter-observer ~~CV~~ ICC ranged from 0.953-0.975~~1.09–4.05%~~ for the measurement of retinal thickness, suggesting that measuring the thickness of each retinal layer by using SD-OCT with reduced speckle noise has good reproducibility.

In normal eyes, the mean thickness of the ONL, IS, and OS was 126, 30, and 56 μm, respectively; these values are consistent with those obtained by Matsumoto et al using SD-OCT (135, 35, and 60 μm, respectively) [21]. Yamada, in a histological study of a human eye (the surgically enucleated eye of a 45-y-old woman), reported that at the fovea, the distance between the ILM and ELM was 150 μm, and at the central fovea, the thickness of the IS and OS was approximately 20–30 μm and 45 μm, respectively [31]. Thus, retinal thickness measured by SD-OCT was identical with that obtained by studying histological sections.

We hypothesize that SRD may cause thinning of the ONL. ONL thickness was significantly lower in eyes with CSC or PCV than in normal eyes, which is consistent with the findings of Matsumoto et al, who reported that ONL thickness was decreased in eyes with CSC [21]. The thickness of the ONL might reflect, at least in part, the volume of the photoreceptors, and so, a reduction in ONL thickness suggests that the volume of the photoreceptors decreases in detached retinas in eyes with CSC or PCV.

~~The changes in the IS may be caused by SRD, fibrin, and hemorrhage. In our subjects, IS thickness was significantly lower in eyes with CSC or PCV than in normal~~

~~eyes. Moreover, IS thickness in eyes with PCV was significantly lower than that in eyes with CSC, suggesting that alterations in IS thickness are more severe in PCV than in CSC. In addition, IS thickness in eyes with fibrin or hemorrhage was significantly lower than that in eyes without fibrin or hemorrhage. Fibrin or hemorrhage are frequently seen in the subretinal fluid in eyes with PCV; this might disturb the IS, resulting in poor vision.~~

The changes in the thickness of the IS layer may be caused by SRD, fibrin deposition, or hemorrhage. In our study, the thickness of the IS layer was significantly lower in the CSC or PCV patients than in the normal individuals. Thickness of the IS layer did not significantly differ between the CSC and PCV in age-matched patients who did not exhibit fibrin deposition or hemorrhage in the subretinal space; therefore, we think that the changes in the thickness of the IS layer may be attributable mainly to the SRD. However, the thickness of the IS layer was significantly lower in the case of PCV patients who exhibited fibrin or hemorrhage than in the case of those who did not exhibit these abnormalities. Fibrin deposition or hemorrhage are frequently observed in the subretinal fluid in the case of PCV patients; this and possibly other factors might cause further damage to the IS layer, resulting in poor vision.

~~OS thickness might reflect the severity of damage to photoreceptors. The OS was significantly less thick in eyes with PCV than in normal eyes, although this difference was not significant between eyes with CSC and normal eyes. Matsumoto et al reported the elongation of the OS in eyes with CSC [21]. We found that the elongation of the OS is frequently seen in eyes with CSC, however rare it may be in eyes with PCV. We postulate 2 reasons to explain these findings. First, the presence of fibrin or hemorrhage in the subretinal space might directly disturb the OS in eyes with PCV, as indicated by our finding that OS thickness was significantly lower in eyes with fibrin or hemorrhage than in eyes without fibrin or hemorrhage. Second, the severe~~

~~damage to the IS might cause the thinning of the OS. It is thought that the OS in detached retinas is elongated because of the lack of phagocytosis by the RPE cells. The OS may elongate in eyes with CSC until the outer segments and RPE are reattached. However, OS thickness was significantly lower in eyes with PCV. Further, as described above, IS thickness was also significantly lower in eyes with PCV than in eyes with CSC. This can be explained as follows: the OS is produced from the IS of photoreceptor cells, and in eyes with PCV, the IS in the detached fovea may be more damaged, resulting in the decreased thickness of the OS.~~

The thickness of the OS layer significantly differed between the PCV and CSC patients. The thickness of the OS layer was significantly lower in the case of PCV patients than in that of normal individuals. However the thickness of the OS layer did not significantly differ between the CSC patients and normal individuals. In the age-matched patients who did not exhibit fibrin deposition or hemorrhage, the thickness of the OS layer was higher in the CSC patients and lower in the case of PCV patients than in that of normal individuals. Matsumoto et al reported elongation of the OS in the eyes of patients with CSC [21]. We found that the OS was frequently elongated in the eyes of the CSC patients; however, this phenomenon may be rare in PCV patients. Thus, the OS in the eyes of CSC patients may elongate until the OSs and RPE are reattached; however, elongation of the OS is not observed in the case of PCV patients. The presence of fibrin or hemorrhage in the subretinal space might have directly damaged the OS in the eyes of the PCV patients, as indicated by our finding that the thickness of the OS layer was significantly lower in the case of patients who exhibited fibrin or hemorrhage than in the case of those who did not exhibit these abnormalities. However, the thickness of the OS layer was decreased even in the case of PCV patients who did not exhibit fibrin or hemorrhage. On the basis of these findings, we postulate 2 hypotheses. First, other factors that possibly exist in the subretinal fluid damaged the

OS in the eyes of the PCV patients. Second, the damage caused to the IS layer may be more severe in the PCV patients than in the CSC patients. The OS is produced from the IS of the photoreceptors; further, in the eyes of the PCV patients, the IS in the detached fovea may be more severely damaged, resulting in the inhibition of OS elongation.

~~Using SD-OCT, we found a differentiating factor between PCV and CSC: the thinning of the IS and OS in eyes with PCV. Some cases of PCV have clinical, FA, IA, or tomographic findings similar to those of CSC; however, the thickness of the IS and OS, as measured using SD-OCT, may help to differentiate between these 2 diseases.~~

~~PCV is most commonly found in individuals over 60 years of age, whereas CSC is usually found in younger individuals. Thus, in the current study, the mean age was significantly different between the CSC and PCV groups. To minimize the bias due to the heterogeneity between the comparison groups, we examined only the older patients and found similar results, although some differences were not found to be significant in this subgroup analysis, probably because of the small population size.~~

PCV is the most common disease occurring in individuals more than 60 years old, whereas CSC occurs in both younger individuals and those above 60 years old. The clinical, FA, IA, or tomographic findings of some PCV cases are similar to those of the CSC. Thus, at times, it is difficult to differentiate CSC and PCV, especially during diagnosis in elderly patients who do not exhibit fibrin deposition or hemorrhage. In the current study, we examined patients who were more than 60 years old and did not exhibit fibrin or hemorrhage (Supplemental Table 1). The thickness of the OS layer significantly increased in the CSC patients and significantly decreased in the PCV patients as compared to that observed in the case of normal individuals. Thus, the thickness of the OS, as measured using SD-OCT, may help in the differential diagnosis of these 2 diseases.

Thinning of the photoreceptor layer may lead to a reduction in VA. Recently,

Matsumoto et al reported that decreased ONL thickness correlates with worse BCVA in eyes with CSC, which is in agreement with our results [32]. Moreover, in the current study, BCVA correlated with the IS thickness at baseline and the last visit, suggesting that the thickness of ONL and IS may be important for visual prognosis in eyes with CSC. On the other hand, thinning of IS and/or OS correlated with worse BCVA in eyes with PCV although the observed correlation was rather weak. Thus, IS thickness may be a common indicator for visual outcomes in CSC and PCV.

We believe that the ELM may act as a barrier for the spread of fibrin or hemorrhage. The zonula adherens between the Müller cells and the photoreceptors at the base of the OS, which make up the ELM, have a very narrow angle [33]. They are not sealed, as are the zonula occludens of the RPE and retinal capillaries, but they do limit the movement of large molecules. Large molecules do not diffuse freely across the retina as they are partially blocked by the ELM [33]. Accordingly, it is reasonable to suppose that the IS and OS are likely to be damaged by fibrin products or hemorrhage in the subretinal space, although these products have a lower influence on the ONL. This may explain why the thickness of the ONL did not differ between eyes with PCV and CSC, whereas that of the IS and OS was lower in eyes with PCV than in eyes with CSC. In eyes with PCV, plasma constituents and exudative products are frequently found in the subretinal fluid, which may disturb the IS and OS. If the inner segments are disturbed, the photoreceptors may be irreversibly altered, which can influence visual function.

In conclusion, SD-OCT with reduced speckle noise allows detailed observation of retinal structures, and thus helps to differentiate between the pathologic features of CSC and PCV. Using SD-OCT, we found thinning of each photoreceptor layer in eyes with PCV compared to normal eyes, and the thinning of the ~~IS and~~ OS in eyes with PCV to be a differentiating factor between PCV and CSC; thus, SD-OCT is helpful in

differentiating CSC from PCV. As compared to CSC, the photoreceptor alterations in PCV were found to be more severe because of the presence of fibrin and hemorrhage in the subretinal space, which correlated with poorer vision.

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References

1. Yannuzzi LA, Sorenson J, Spaide RF, Lipson B (1990) Idiopathic polypoidal choroidal vasculopathy (IPCV). Retina 10:1-8.
2. Yannuzzi LA, Wong DW, Sforzolini BS, Goldbaum M, Tang KC, Spaide RF, Freund KB, Slakter JS, Guyer DR, Sorenson JA, Fisher Y, Maberley D, Orlock DA (1999) Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol 117**:**1503-1510.
3. Yannuzzi LA, Ciardella A, Spaide RF, Rabb M, Freund KB, Orlock DA (1997) The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. Arch Ophthalmol 115:478-485.
4. Sasahara M, Tsujikawa A, Musashi K, Gotoh N, Otani A, Mandai M, Yoshimura N (2006) Polypoidal choroidal vasculopathy with choroidal vascular hyperpermeability. Am J Ophthalmol 142:601-607.
5. Yannuzzi LA, Freund KB, Goldbaum M, Scassellati-Sforzolini B, Guyer DR, Spaide RF, Maberley D, Wong DW, Slakter JS, Sorenson JA, Fisher YL, Orlock DA (2000) Polypoidal choroidal vasculopathy masquerading as central serous chorioretinopathy. Ophthalmology 107:767-777.

6. Moorthy RS, Lyon AT, Rabb MF, Spaide RF, Yannuzzi LA, Jampol LM (1998) Idiopathic polypoidal choroidal vasculopathy of the macula. Ophthalmology 105:1380-1385.
7. Yannuzzi LA, Shakin JL, Fisher YL, Altomonte MA (1984) Peripheral retinal detachments and retinal pigment epithelial atrophic tracts secondary to central serous pigment epitheliopathy. Ophthalmology 91:1554-1572.
8. Levine R, Brucker AJ, Robinson F (1989) Long-term follow-up of idiopathic central serous chorioretinopathy by fluorescein angiography. Ophthalmology 96:854-859.
9. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D (1994) Digital indocyanine green videoangiography of central serous chorioretinopathy. Arch Ophthalmol 112:1057-1062.
10. Piccolino FC, Borgia L (1994) Central serous chorioretinopathy and indocyanine green angiography. Retina 14:231-242.
11. Scheider A, Nasemannn JE, Lund OE (1993) Fluorescein and indocyanine green angiographies of central serous choroidopathy by scanning laser ophthalmoscopy. Am J Ophthalmol 115:50-56.
12. Prunte C, Flammer J (1996) Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 121:26-34.
13. Iida T, Kishi S, Hagimura N, Shimizu K (1999) Persistent and bilateral choroidal vascular abnormalities in central serous chorioretinopathy. Retina 19:508-512.
14. Fujimoto H, Gomi F, Wakabayashi T, Sawa M, Tsujikawa M, Tano Y (2008) Morphologic changes in acute central serous chorioretinopathy evaluated by Fourier-domain optical coherence tomography. Ophthalmology 115:1494-1500.
15. Wojtkowski M, Srinivasan V, Fujimoto JG, Ko T, Schuman JS, Kowalczyk A, Duker JS (2005) Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. Ophthalmology 112:1734-1746.

16. Hangai M, Ojima Y, Gotoh N, Inoue R, Yasuno Y, Makita S, Yamanari M, Yatagai T, Kita M, Yoshimura N (2007) Three-dimensional imaging of macular holes with high-speed optical coherence tomography. Ophthalmology 114:763-773.

17. Ooto S, Hangai M, Sakamoto A, Tomidokoro A, Araie M, Otani T, Kishi S, Matsushita K, Maeda N, Shirakashi M, Abe H, Takeda H, Sugiyama K, Saito H, Iwase A, Yoshimura N (2010) Three-dimensional profile of macular retinal thickness in normal Japanese eyes. Invest Ophthalmol Vis Sci 51:465-473.

18. Sakamoto A, Hangai M, Yoshimura N (2008) Spectral-domain optical coherence tomography with multiple B-scan averaging for speckle-noise-reduced imaging of retinal diseases. Ophthalmology 115:1071-1078.

19. Spaide RF, Klancnik JM Jr (2005) Fundus autofluorescence and central serous chorioretinopathy. Ophthalmology 112:825-833.

20. Iida T, Hagimura N, Sato T, Kishi S (2000) Evaluation of central serous chorioretinopathy with optical coherence tomography. Am J Ophthalmol 129:16-20.

21. Matsumoto H, Kishi S, Otani T, Sato T (2008) Elongation of photoreceptor outer segment in central serous chorioretinopathy. Am J Ophthalmol 145:162-168.

22. Ojima Y, Hangai M, Sasahara M, Gotoh N, Inoue R, Yasuno Y, Makita S, Yatagai T, Tsujikawa A, Yoshimura N (2007) Three-dimensional imaging of the foveal photoreceptor layer in central serous chorioretinopathy using high-speed optical coherence tomography. Ophthalmology 114:2197-2207.

23. Iijima H, Imai M, Gohdo T, Tsukahara S (1999) Optical coherence tomography of idiopathic polypoidal choroidal vasculopathy. Am J Ophthalmol 127:301-305.

24. Iijima H, Iida T, Imai M, Tsukahara S (2000) Optical coherence tomography of orange-red subretinal lesions in eyes with idiopathic polypoidal choroidal

vasculopathy. Am J Ophthalmol 129:21-26.

25. Sato T, Kishi S, Watanabe G, Matsumoto H, Mukai R (2007) Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. Retina 27:589-594.

26. Kameda T, Tsujikawa A, Otani A, Sasahara M, Gotoh N, Tamura H, Yoshimura N (2007) Polypoidal choroidal vasculopathy examined with en face optical coherence tomography. Clin Experiment Ophthalmol 35:596-601.

27. Kon Y, Iida T, Maruko I, Saito M (2008) The optical coherence tomography-ophthalmoscope for examination of central serous chorioretinopathy with precipitates. Retina 28:864-869.

28. Tsujikawa A, Sasahara M, Otani A, Gotoh N, Kameda T, Iwama D, Yodoi Y, Tamura H, Mandai M, Yoshimura N (2007) Pigment epithelial detachment in polypoidal choroidal vasculopathy. Am J Ophthalmol 143:102-111.

29. Ojima Y, Hangai M, Sakamoto A, Tsujikawa A, Otani A, Tamura H, Yoshimura N (2009) Improved visualization of polypoidal choroidal vasculopathy lesions using spectral-domain optical coherence tomography. Retina 29:52-59.

30. Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK, Iliev ME, Frey M, Rothenbuehler SP, Enzmann V, Wolf S (2009) Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. Invest Ophthalmol Vis Sci 50:3432-3437.

31. Yamada E (1969) Some structural features of the fovea centralis in the human retina. Arch Ophthalmol 82:151-159.

32. Matsumoto H, Sato T, Kishi S (2009) Outer nuclear layer thickness at the fovea determines visual outcomes in resolved central serous chorioretinopathy. Am J Ophthalmol. 148:105-110.

33. Marmor MF (1999) Mechanisms of fluid accumulation in retinal edema. Doc

Ophthalmol 97:239-249.

Figure Legends

Figure 1. Spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise of a normal eye (eye of a 60-y-old man whose best-corrected visual acuity was 1.5 with -1.5 diopters of myopia). **A**, Horizontal scan through the fovea centralis obtained at a 30^{o} angle width. **B**, Magnified view. SD-OCT with reduced speckle noise showed 4 highly reflective lines in this normal eye, namely, the external limiting membrane (ELM), the junction between the photoreceptor inner and outer segments (IS/OS), an intermediate reflective line between the IS/OS line and retinal pigment epithelium (RPE), and the RPE. Thickness of the outer nuclear layer (ONL), which is the distance between the outer border of the inner limiting membrane and the ELM, is 131 μm. Thickness of the inner segment (IS), which is the distance between the ELM and the inner border of the IS/OS, is 30 μm. Thickness of the outer segment (OS), which is the distance between the inner borders of the IS/OS and RPE, is 62 μm.

Figure 2. Ophthalmologic examination of the eye of a 57-y-old man with central serous chorioretinopathy (CSC) and a 1-mo history of decreased visual acuity (VA) in the right eye; his VA was 0.7.

At the baseline. **A**, Funduscopic examination shows subretinal fluid. **B**–**E**, Early-phase (**B**) and mid-phase (**D**) fluorescein angiography (FA) shows intense leakage in an inkblot pattern. Early-phase (**C**) and mid-phase (**E**) indocyanine green angiography (IA) do not show polypoid lesions. Hyperfluorescent area corresponds to a leaking point seen using FA. **F**, Vertical scan through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in C. Spectral-domain optical coherence tomography (SD-OCT) image shows serous retinal detachment. **G**, Magnified view of F. Thickness of the outer nuclear layer (ONL) is 88 μm, that of the

inner segment (IS) is 22 μm, and that of the outer segment (OS) is 56 μm.
After 2 mo, the retina attached spontaneously.
At last follow-up (after 12 mo), the man's VA was 1.5. **H**, Vertical scan through the fovea centralis obtained at a 30° angle width. Resolved serous retinal detachment. **I**, Magnified view of H. Thickness of the ONL is 88 μm, that of the IS is 22 μm, and that of the OS is 46 μm.

Figure 3. Ophthalmologic examination of the eye of a 71-y-old man with polypoidal choroidal vasculopathy (PCV) and a 2-mo history of decreased visual acuity (VA) in right eye; his VA was 0.2.
At the baseline. **A**, Funduscopic examination shows subretinal hemorrhage, subretinal fluid, and reddish-orange nodules. **B** and **C**, Simultaneously obtained fluorescein angiography (FA) (**B**) and indocyanine green angiography (IA) (**C**) images. IA shows a small branching vascular network that terminates in polypoid lesions. **D**, Horizontal scan through the fovea centralis obtained at a 30° angle width, corresponding to the arrow indicated in C. Spectral-domain optical coherence tomography (SD-OCT) image shows serous retinal detachment and polypoid lesions. **E**, Magnified view of D. Thickness of the outer nuclear layer (ONL) is 70 μm, that of the inner segment (IS) is 15 μm, and that of the outer segment (OS) is 22 μm.
Photodynamic therapy combined with intravitreal triamcinolone acetonide and bevacizumab was given to the patient. After 2 mo, serous retinal detachment resolved. At last follow-up (after 6 mo), the patient's VA was 0.2. **F**, Horizontal scan through the fovea centralis obtained at a 30° angle width shows that the serous retinal detachment has resolved. **G**, Magnified view of F. Thickness of the ONL is 62 μm, that of the IS is 14 μm, and that of the OS is 11 μm.

Figure 4. Comparison of the inner segments (IS) and outer segments (OS) in eyes with central serous chorioretinopathy (CSC) and polypoidal choroidal vasculopathy (PCV).

A, Ophthalmologic examination of the eye of a 37-y-old man with CSC and 1-mo history of visual disturbance; his visual acuity (VA) was 1.0. (Left) Funduscopic examination shows serous retinal detachment. (Right) Mid-phase fluorescein angiography shows leakage in a smokestack pattern. **B**, Horizontal line scan through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in **A**. Image obtained using spectral-domain optical coherence tomography (SD-OCT) with reduced speckle noise shows elongation of the OS.

C, Ophthalmologic examination of the eye of a 64-y-old man with PCV and 1-mo history of visual disturbance; his VA was 0.8. (Left) Funduscopic examination shows serous retinal detachment, pigment epithelial detachment, and reddish-orange nodules. However, fibrin or hemorrhage are not seen in the subretinal space. (Right) Indocyanine green angiography (IA) shows a small branching vascular network that terminates in polypoid lesions. The hypofluorescent area corresponds to serous retinal detachment. **D**, Vertical line scan of SD-OCT with reduced speckle noise through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in **C**. Thickness of IS and OS are relatively unchanged.

E, Ophthalmologic examination of the eye of a 60-y-old woman with PCV and 2-mo history of visual disturbance; her VA was 0.2. (Left) Funduscopic examination shows serous retinal detachment, reddish-orange nodules, fibrin, and hemorrhage in the subretinal space (arrow). (Right) IA shows a small branching vascular network that terminates in polypoid lesions. FE, Vertical line scan through the fovea centralis obtained at a 30^{o} angle width, corresponding to the arrow indicated in **D**. High reflectivity area suggesting fibrin or hemorrhage is observed in the subretinal space

(arrow). SD-OCT with reduced speckle noise shows the thinning of the IS and OS.

ELM = external limiting membrane

Table (edit on)

Table 1. Patient Characteristics and Fundus Findings

	CSC (n = 36)	PCV (n = 23)	*P* value
Men/Women (n)	31/5	17/6	0.245*
Age (y) mean +/- 1 SD	49.0 ± 11.3 (37~73)	71.3 ± 8.2 (57~92)	<0.001†
Follow-up period (mo) mean +/- 1 SD	7.1 ± 3.4 (3~15)	9.0 ± 4.1 (3~16)	~~0.098~~<0.001†
Median duration of symptoms	3.0 mo (2 wk~4 y)	3.0 mo (1 mo~6 y)	
Mean height of SRD at fovea (μm) mean +/- 1 SD	191 ± 107	185 ± 111	0.~~859~~971†
Mean distance from fovea to nearest point of attachment to the retina (μm) mean +/- 1 SD	1427 ± 542	1710 ± 573	0.~~121~~090†
Fibrin	7/36 (19%)	13/23 (57%)	0.001*
Subretinal hemorrhage	0/36 (0%)	15/23 (65%)	<0.001*
Mean logMAR at baseline	0.13	0.36	0.~~024~~006†
Resolution of SRD at last follow-up	23/36 (64%)	15/23 (65%)	0.918*
Mean logMAR at last follow-up	0.06	0.28	0.~~032~~007

			†

*Fisher's exact test, †~~Unpaired *t*-test~~Tukey-Kramer test.

CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, SRD = serous retinal detachment, SD=standard deviation, log MAR=logarithm of minimal angle of resolution

y=year, mo=month, and wk=week

Table 2. Inter-observer Reproducibility of the Measurement of Retinal Thickness Using SD-OCT with Reduced Speckle Noise: ~~Coefficients of Variation (%)~~Intraclass Correlation Coefficient

	Normal (n = 44)	CSC (n = 36)	PCV (n = 23)
ONL	~~1.57~~0.972	~~1.93~~0.969	~~2.52~~0.963
IS	~~2.00~~0.970	~~2.58~~0.964	~~2.88~~0.961
OS	~~1.09~~0.975	~~3.59~~0.958	~~4.05~~0.953

SD-OCT = spectral-domain optical coherence tomography, CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, ONL = outer nuclear layer, IS = inner segment, and OS = outer segment.

Table 3. Retinal Thickness at the Baseline and at Last Follow-up

		Retinal thickness (μm)					
		Normal (n = 44)	**CSC (n = 36)**	***P* value***	**PCV (n = 23)**	***P* value†**	***P* value**
ONL	baseline mean +/- 1 SD	126 ± 23 (88~187)	88 ± 21 (52~136)	<0.001	89 ± 26 (32~140)	<0.001	0.998‡
	last follow-up mean +/- 1 SD		84 ± 22 (39~136)		87 ± 28 (30~139)		0.747§
IS	baseline mean +/- 1 SD	30 ± 5 (21~38)	21 ± 4 (8~28)	<0.001	18 ± 6 (8~29)	<0.001	0.034‡
	last follow-up mean +/- 1 SD		20 ± 4 (8~26)		17 ± 5 (6~29)		0.018§
OS	baseline mean +/- 1 SD	56 ± 6 (40~68)	62 ± 28 (14~137)	0.394	33 ± 16 (14~68)	<0.001	<0.001‡
	last follow-up		54 ± 36 (11~134)		30 ± 14 (6~58)		0.004§

	mean +/- 1 SD

*Tukey-Kramer test, *P* value of normal eyes and eyes with CSC.

†Tukey-Kramer test, *P* value of normal eyes and eyes with PCV.

‡Tukey-Kramer test, *P* value of eyes with CSC and PCV.

§Unpaired *t*-test, *P* value of eyes with CSC and PCV.

CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, ONL = outer nuclear layer, IS = inner segment, OS = outer segment, and SD=standard deviation

Table 4. Comparison of Retinal Thickness and Visual Acuity between Eyes with PCV, with or without the Presence of Subretinal Fibrin or Hemorrhage.

	Fibrin or Hemorrhage (-) (n = 8)	**Fibrin or Hemorrhage (+) (n = 15)**	***P* value***
ONL (μm) mean +/- 1 SD	90 ± 32	88 ± 23	0.872
IS (μm) mean +/- 1 SD	22 ± 5	15 ± 4	0.001
OS (μm) mean +/- 1 SD	43 ± 19	27 ± 12	0.022
logMAR	0.136	0.477	0.035

*Unpaired *t*-test

PCV = polypoidal choroidal vasculopathy, SRH = subretinal hemorrhage, ONL = outer nuclear layer, IS = inner segment, and OS = outer segment, and SD=standard deviation, log MAR=logarithm of minimal angle of resolution

Supplemental Table (edit on)

Supplemental Table 1. Retinal Thickness at the Baseline and at Last Follow-up in Subjects over 60 Years Old without Fibrin or Hemorrhage in the Subretinal Space

		Retinal thickness (μm)					
		Normal (n = 42)	**CSC (n = 67)**	***P* value***	**PCV (n = 226)**	***P* value†**	***P* value**
ONL	baseline mean +/- 1 SD	126 ± 23	82± 177	<0.001	868 ± 206	<0.001	0.7870.966‡
	last follow-up mean +/- 1 SD		82 ± 110		87 ± 208		0.6890.539§
IS	baseline mean +/- 1 SD	30 ± 5	221 ± 3	<0.0041	2018 ± 67	<0.001	0.2420.637‡
	last follow-up mean +/- 1 SD		21 ± 34		187 ± 46		0.1150.066§
OS	baseline mean +/- 1 SD	56 ± 6	731 ± 336	0.2220.016	372 ± 1620	<0.0031	0.054<0.001‡
	last follow-up mean +/- 1 SD		463 ± 167		2631 ± 915		0.1070.025§

*Tukey-Kramer test, *P* value of normal eyes and eyes with CSC.

†Tukey-Kramer test, *P* value of normal eyes and eyes with PCV.

‡Tukey-Kramer test, *P* value of eyes with CSC and PCV.

§Unpaired *t*-test, *P* value of eyes with CSC and PCV.

CSC = central serous chorioretinopathy, PCV = polypoidal choroidal vasculopathy, ONL = outer nuclear layer, IS = inner segment, OS = outer segment, SD=standard deviation