中心性漿液性脈絡網膜症における Loculation of Fluid の存在に関わる臨床要因

学位論文

Clinical Factors Related to Loculation of Fluid in Central Serous Chorioretinopathy

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Clinical Factors Related to Loculation of Fluid in Central Serous Chorioretinopathy

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• PURPOSE: To elucidate clinical factors related to the presence of loculation of fluid (LOF) in the posterior choroid in central serous chorioretinopathy (CSC).
• DESIGN: Retrospective, cross-sectional study.
• METHODS: This single-center study included 158 eyes from 158 patients with CSC who were classified into LOF and non-LOF groups. The groups were compared for age, sex, spherical equivalent, axial length, subfoveal choroidal thickness (SCT), and scleral thickness. Using swept-source optical coherence tomography (OCT), we determined the presence of LOF based on B-scan and en face images. Scleral thickness was measured 6 mm posterior to the scleral spur in 4 directions using anterior-segment OCT.
• RESULTS: The 158 eyes were classified into 98 eyes in the LOF group and 60 eyes in the non-LOF group. In univariable analyses, the LOF group was younger ($P = .01$) and had a higher male ratio ($P = .03$) and greater SCT ($P < .001$) than the non-LOF group. All scleral thicknesses at the superior, temporal, inferior, and nasal points were greater in the LOF group than in the non-LOF group (426.2 vs 395.1 μm, 445.7 vs 414.9 μm, 459.2 vs 428.8 μm, 445.4 vs 414.3 μm, all $P < .05$). Multivariable analyses found that SCT (odds ratio [OR] 1.02, 95% CI 1.01-1.02, $P < .001$) and mean scleral thickness (OR 1.02, 95% CI 1.02-1.03, $P = .002$) were significantly associated with the presence of LOF.
• CONCLUSION: A thick choroid and thick sclera appeared to be related to the presence of LOF in CSC. (Am J Ophthalmol 2022;235: 197–203. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

Central serous chorioretinopathy (CSC) is a common disorder characterized by serous retinal detachment in the posterior pole of the eye[1] and one of the manifestations of pachychoroid spectrum diseases.[2] Although it is widely known that the risk factors for CSC include male sex,[3-5] psychological stress,[6] type A personality,[7] pregnancy,[4] steroid use,[4] hyperopic refractive error,[5,8,9] short axial length,[8,9] and genetic factors,[1] the exact pathophysiology of CSC remains unclear.

Advanced research in optical coherence tomography (OCT), especially enhanced depth imaging (EDI) OCT[10] and high-penetration swept-source (SS) OCT,[11] has made it possible to observe the choroidal structures in the posterior pole. Using these OCT techniques, subfoveal choroidal thickness (SCT) has been proven to be significantly greater in eyes with CSC than in normal eyes.[12] In addition, the vascular lumens of the larger vessels in the outer choroid are reportedly dilated in CSC eyes.[13,14]

Using EDI-OCT, Spaide and Ryan[15] found peculiar hyporeflective areas in the outer choroid and suprachoroidal space in eyes with CSC and named this feature loculation of fluid (LOF) in the posterior choroid. The authors demonstrated that eyes with LOF had a thicker subfoveal choroid compared with those without LOF and concluded that LOF was seemingly a potential accumulation of fluid that went beyond the limit of saturation of the choroidal stroma.[15] The accumulation of fluid in the suprachoroidal space that is located between the choroid and the sclera is similar to that in uveal effusion syndrome (UES) with nanophthalmos or a thick sclera.[16,17]

Recently, we reported that scleral thickness measured by anterior-segment (AS) OCT was significantly greater in CSC eyes than in normal control eyes.[18] Therefore, similar to UES, a thick sclera in CSC eyes may cause not only outflow disturbance of the vortex veins in the scleral tunnels but also reduce the transscleral fluid outflow.[18] However, the onset mechanism of LOF and its relationship with a thick sclera have not been clarified. To elucidate the relationship between LOF and a thick sclera, we investigated clinical factors related to the presence of LOF in the posterior choroid in CSC.

METHODS

This retrospective comparative study was conducted at a single institution. The study procedures were carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of the

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Ryukyus Hospital (approval number: 1503). Informed consent was obtained from all the participants after explaining the study protocol. This study included 158 eyes of 158 patients with CSC initially seen at the University of the Ryukyus Hospital between October 2018 and November 2020. The data of all consecutive patients with CSC who consulted during the study period were retrospectively reviewed.

CSC diagnosis was based on the presence of subretinal fluid in the posterior pole associated with dye leakage from the retinal pigment epithelium on fluorescein angiography. In addition, indocyanine green angiography showed multifocal choroidal vascular hyperpermeability in the late phase. The exclusion criteria were as follows: other retinal diseases associated with subretinal fluid, glaucoma, ocular hypertension or hypotony ($\geq$21 and $\leq$5 mm Hg, respectively), trauma, uveitis, scleritis, infection, history of intraocular surgery, history of photodynamic therapy, history of systemic corticosteroid use, and history of systemic conditions associated with CSC. In bilateral CSC, the right eyes were selected for analysis.

At the initial examination, all 158 patients with CSC underwent an extensive ophthalmic assessment with refraction, decimal best-corrected visual acuity testing with Landolt C charts (SC-1000; TOMEY), measurement of axial length, slit-lamp biomicroscopy with a contact lens or noncontact lens, color fundus photography, fluorescein angiography, indocyanine green angiography, fundus autofluorescence photography, SS OCT, and AS OCT. Objective refraction was measured using an autorefractor (ARK-1a; NIDEK). The spherical equivalent (SE) was defined as the sum of the spherical power and half of the cylinder power. Axial length (AL) was measured using an interferometer (IOL Master 700; Carl Zeiss Meditec). Color fundus photography was performed using a fundus camera system (TRC-50DX; Topcon). Fluorescein angiography and indocyanine green angiography were performed using a confocal scanning laser ophthalmoscope (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). Cross-sectional images of the macular area were obtained using SS OCT (DRI-OCT Triton; Topcon). We measured the SCT using horizontal B-scans through the fovea. SCT was calculated by measuring the vertical distance between the hyperreflective line corresponding to Bruch membrane beneath the retinal pigment epithelium and the inner scleral border under the fovea, using the caliper function of SS OCT. We measured scleral thickness using second-generation SS-AS OCT (CASIA 2; TOMEY). Scleral thickness was manually analyzed under the rectus muscles based on the methods reported in our previous study using AS OCT.[18] First, the 4 rectus muscles (superior, lateral, inferior, and medial rectus muscles) were detected as low reflective bands by gazing in the opposite direction of the targeted muscle and were differentiated from the sclera visualized as a highly reflective band. Second, we determined the upper scleral line based on the low reflectivity of each rectus muscle and identified the posterior scleral boundary from the signal originating from the choroid (Figure 1). The AS OCT scans were taken parallel to each rectus muscle with a diameter of 16 mm. The raster scan mode consisting of 16 B-scans with a width of 4 mm was applied, and scleral thickness was measured at the center of each rectus muscle. Finally, scleral thickness was measured vertically 6 mm posterior to the scleral spur in 4 directions: superior, temporal, inferior, and nasal.

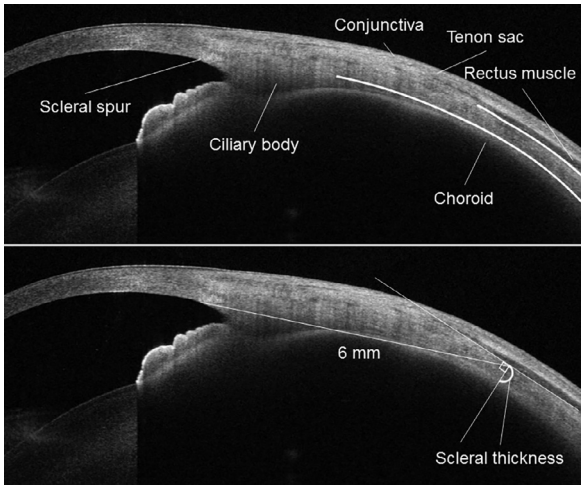

FIGURE 1. Anterior-segment optical coherence tomography images by gazing in 4 directions were used to measure scleral thickness. (Top) The upper scleral line was determined based on the low brightness of each rectus muscle and the lower scleral line delineated from the difference in brightness between the sclera and choroid. (Bottom) The scleral thickness was vertically measured 6 mm posterior to the scleral spur. Scleral thickness was measured in 4 directions (superior, temporal, inferior, and nasal).

As for the presence or absence of LOF, we referred to the method previously described by Spaide and Ryan.[15] The authors mainly used spectral-domain OCT, whereas we used SS OCT to determine the presence or absence of LOF. The SS OCT we used adopted a tunable laser with a central wavelength of 1050 nm that provides excellent tissue penetration and high-definition imaging of the retina and choroid. In addition, the SS OCT acquires 100 000 A-scans per second, with an axial resolution of 8 μm and a lateral resolution of 20 μm. Using SS OCT, volume scan data were acquired with a raster scan protocol of 512 $\times$ 256 (horizontal $\times$ vertical) B-scans, capturing the 12 $\times$ 9-mm area centered at the middle point between the foveal center and the optic disc. We acquired en face images using coronal slices from a 3-dimensional data set using the EnView software (Enview) installed on the SS OCT. The en face image was flattened at the level of the Bruch membrane. The presence of LOF was determined by 2 retinal specialists (NI and NT). The presence of LOF on B-scans was defined as hyporeflective areas in the outer choroid and the suprachoroidal space,

TABLE 1. Characteristics of Patients With Central Serous Chorioretinopathy in the LOF and Non-LOF Groups

Characteristics	LOF Group	Non-LOF Group	*P* Value
Number of eyes (%)	98 (62.0)	60 (38.0)	
Age (y)	50.2 ± 10.9	55.1 ± 12.7	.010[a]
Male sex, n (%)	86 (87.8)	44 (73.3)	.030[b]
Spherical equivalent (diopters)	–0.33 ± 1.99	–0.98 ± 2.13	.100[a]
Axial length (mm)	23.59 ± 0.89	23.78 ± 1.00	.400[a]
Subfoveal choroidal thickness (μm)	448.2 ± 89.1	325.9 ± 81.2	<.001[a]
Scleral thickness (μm)			
Superior	426.2 ± 63.0	395.1 ± 52.1	.003[a]
Temporal	445.7 ± 55.9	414.9 ± 47.4	<.001[a]
Inferior	459.2 ± 62.3	428.8 ± 49.6	.004[a]
Nasal	445.4 ± 59.3	414.3 ± 55.9	.004[a]

LOF = loculation of fluid.
[a]Wilcoxon rank sum test.
[b]Fisher exact test.Unless otherwise noted, values are mean ± SD.

TABLE 2. Multivariable Analysis for the Presence of Loculation of Fluid in Patients With Central Serous Chorioretinopathy

	Odds ratio	95% CI	*P* Value
Mean age	0.99	0.95-1.04	.830
Female sex	0.72	0.23-2.33	.590
Axial length	1.01	0.60-1.68	.980
Subfoveal choroidal thickness	1.02	1.01-1.02	<.001
Mean value of scleral thicknesses in 4 directions	1.02	1.02-1.03	.002

larger topographically than the large choroidal vessels, an angular inner border, and no bounding vascular wall.[15] Additionally, the LOF was reconfirmed by en face images to be free of connections to horizontal and vertical choroidal vessels.

The patients were divided into 2 groups: patients with LOF (LOF group) and those without LOF (non-LOF group). Age, sex, SE, AL, SCT, and scleral thickness were compared between the LOF and non-LOF groups. Data were analyzed using frequency and descriptive statistics. The Wilcoxon rank-sum test was used to analyze age, SE, AL, SCT, and scleral thickness. Fisher exact test was used to analyze sex. To investigate the factors related to the presence of LOF, we used multivariable logistic regression to control for the potentially confounding roles of age, sex, AL, SCT, and the mean value of scleral thicknesses in 4 directions. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc). All values are expressed as mean ± standard deviation. *P* values less than .05 indicated statistical significance.

RESULTS

The 158 eyes were classified into 98 eyes in the LOF group and 60 eyes in the non-LOF group. The clinical characteristics of the 2 groups are summarized in Table 1. In the univariable analyses, patients in the LOF group were significantly younger (50.2 ± 10.9 vs 55.1 ± 12.7 years; $P = .01$) and had a higher male ratio (87.8% vs 73.3%; $P = .03$). SCT was significantly greater in the LOF group than in the non-LOF group (448.2 ± 89.1 vs 325.9 ± 81.2 μm; $P < .001$). All scleral thicknesses were significantly greater in the LOF group than in the non-LOF group at the superior (426.2 ± 63.0 vs 395.1 ± 52.1 μm; $P = .003$), temporal (445.7 ± 52.9 vs 414.9 ± 47.4 μm; $P < .001$), inferior (459.2 ± 62.3 vs 428.8 ± 49.6 μm; $P = .004$), and nasal (445.4 ± 59.3 vs 414.3 ± 55.9 μm; $P = .004$) points. No significant differences were found in SE and AL between the 2 groups. Table 2 presents the adjusted odds ratios (ORs) of CSC patients with LOF for each variable, as listed in Table 1. The variables used in the multivariable analysis were clinical factors predicted to be associated with LOF: age, sex, SCT, and the mean value of scleral thicknesses in 4 directions. SCT and the mean scleral thickness independently demonstrated a high risk of LOF, with an adjusted OR of 1.02 for SCT (95% CI 1.01-1.02, $P < .001$) and 1.02 for the mean scleral thickness (95% CI 1.02-1.03, $P = .002$). Representative LOF case and non-LOF case are shown in Figures 2 and 3 and Figures 4 and 5, respectively.

DISCUSSION

Using multimodal imaging, the clinical factors related to LOF in CSC patients were examined, and a thick choroid

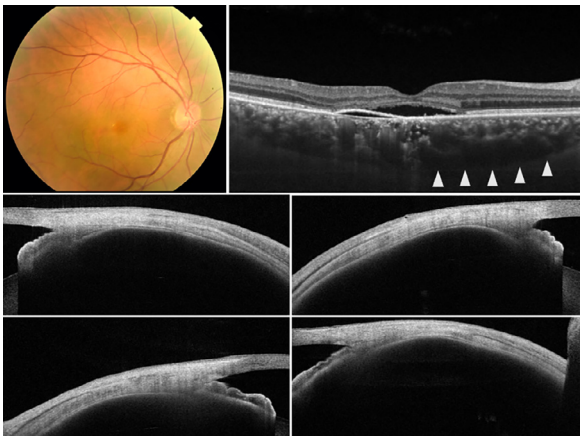

FIGURE 2. Right eye of a 51-year-old man with central serous chorioretinopathy. The spherical equivalent was 0.125 diopter, and the axial length was 24.12 mm. (Top left) Color fundus photograph revealed serous retinal detachment in the macula. (Top right) Horizontal B-scan with swept-source optical coherence tomography (OCT) image showing serous retinal detachment and pigment epithelial detachment. Subfoveal choroidal thickness was 475 μm. Dilation of choroidal vessels under the fovea was observed. Loculation of fluid was present in the outer choroid (white arrowheads). Cross-sectional images of the sclera in 4 directions—temporal (middle left), nasal (middle right), inferior (bottom left), and superior (bottom right)—were obtained using anterior segment OCT. Scleral thickness at the temporal, nasal, inferior, and superior points was 481, 483, 514, and 459 μm, respectively.

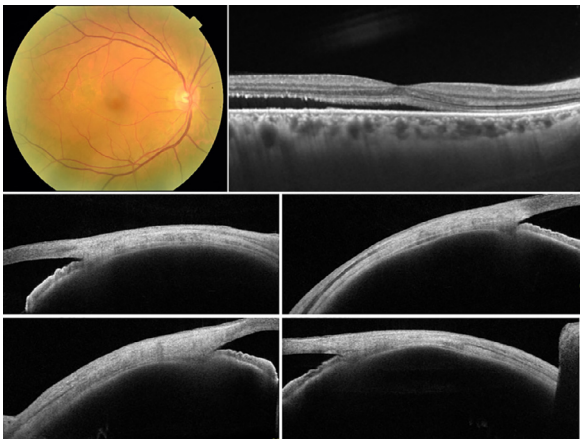

FIGURE 4. Right eye of a 52-year-old man with central serous chorioretinopathy. The spherical equivalent was –1.25 diopter, and the axial length was 23.59 mm. (Top left) Color fundus photograph revealed serous retinal detachment that expanded temporally. (Top right) Horizontal B-scan with swept-source optical coherence tomography (OCT) image showing shallow serous retinal detachment. The subfoveal choroidal thickness was 282 μm. Dilation of choroidal vessels under the fovea was unremarkable. There was no loculation of fluid on the B-scan. Cross-sectional images of sclera in 4 directions—temporal (middle left), nasal (middle right), inferior (bottom left), and superior (bottom right)—were obtained using anterior segment OCT. Scleral thickness at the temporal, nasal, inferior, and superior points was 363, 376, 384, and 353 μm, respectively.

and thick sclera were found to be independently associated with the presence of LOF. To our knowledge, no previous studies have reported these results in CSC. These findings suggest that both a thick choroid and thick sclera may play a role in the presence of LOF in CSC.

LOF has been reported to be a manifestation of excessive fluid accumulation in the outer choroid and the suprachoroidal space.[15] In this study, the presence of LOF was confirmed using SS OCT. SS OCT adopts a central wavelength of 1050 nm and is considered to have better tissue penetration. Our results revealed that the proportion of LOF in CSC eyes was 62.0%, whereas Spaide and Ryan[15]

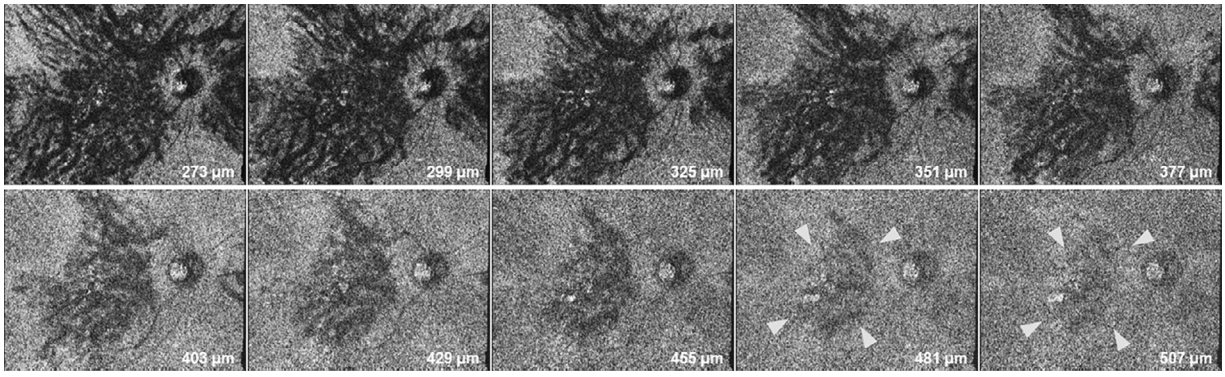

FIGURE 3. En face images of the case in Figure 2. Volume scan data captured the 12 × 9-mm area centered at the middle point between the foveal center and the optic disc. The en face image was flattened at the level of the Bruch membrane. These en face images show the outside of Bruch membrane from 273 to 507 μm at intervals of 26 μm. Loculation of fluid exists under the outer choroid and was confirmed to be free from connections to horizontal and vertical choroidal vessels using en face images (white arrowheads).

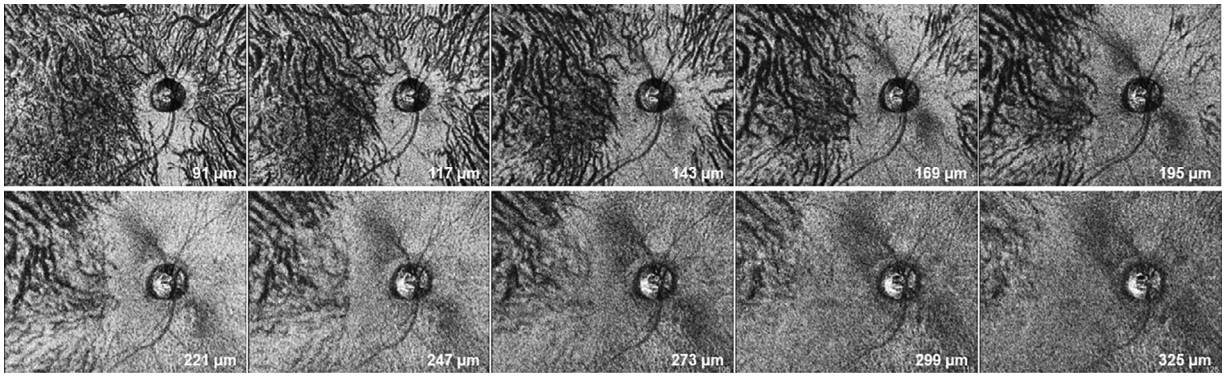

FIGURE 5. En face images of the case in Figure 4. Volume scan data captured the 12 × 9-mm area centered at the middle point between the foveal center and the optic disc. The en face image was flattened at the level of the Bruch membrane. These en face images show the outside of Bruch membrane from 91 to 325 µm at intervals of 26 µm. Loculation of fluid is not present in en face images.

reported a ratio of 64.8%. Therefore, our results using SS OCT were comparable with those in the previous study by Spaide and Ryan[15] in which they mainly used spectral-domain OCT. The authors also reported that 78.9% of cases with SCT greater than 403 µm had LOF.[15] In the current study, LOF was found in 86.1% of cases with SCT greater than 403 µm. Although some patients with CSC did not present with serous retinal detachment in the study by Spaide and Ryan, all CSC patients in the current study presented with serous retinal detachment. The difference in the prevalence of LOF in eyes with SCT greater than 403 µm may be related to the fact that we examined patients with active disease.

In the present study, SCT was significantly greater in CSC eyes with LOF than in those without LOF, as reported by Spaide and Ryan.[15] In addition, SCT was significantly associated with the presence of LOF in the multivariable logistic regression analysis. Choroidal thickness is reportedly affected by many factors such as age,[19] AL,[20] and even circadian variation.[21] As previously demonstrated, a thick choroid is a well-known indicator of CSC.[12] Furthermore, photodynamic therapy with verteporfin as a CSC treatment causes a decrease in choroidal thickness.[22,23] Based on these results, it is conceivable that the choroid has some fluid-holding and expansion function. However, if the fluid retention in the vascular plexus exceeds the limit, the excessive fluid components may leak into the choroidal stroma and eventually flow into the subretinal space. Our results showed that the abnormal accumulation of fluid that goes beyond the limit in CSC eyes with LOF might be a manifestation of excessive fluid at least partially accumulated in the choroidal stroma and the suprachoroidal space.

In the current study, we decided to measure scleral thickness 6 mm posterior to the scleral spur. Currently, we cannot measure scleral thickness in the posterior pole using OCT, except for several specific conditions such as a dome-shaped macula,[24] tilted disc syndrome,[25] and pathologic myopia.[26] From several reports on enucleated globes, it can be speculated that the anterior and posterior segment scleral thickness measurements are correlated with each other.[27,28] Although the measurement positions in this study were in close proximity to the ora serrata,[29] it may reflect the scleral thickness in the posterior segment as shown by histomorphometric studies.[27,28]

Recently, we reported that scleral thickness is significantly greater in CSC eyes than in normal control eyes using AS OCT and concluded that a thick sclera may have a role in the pathogenesis of CSC.[18] The current study revealed that anterior scleral thickness was significantly greater in the LOF group than in the non-LOF group at the superior, temporal, inferior, and nasal points, and the mean value of scleral thickness was significantly associated with the presence of LOF, even after multivariate analysis. A thick sclera possibly reduces the transscleral fluid outflow, and excessive fluid cannot leave through the sclera. Additionally, the thick sclera may compress the vortex veins in the scleral tunnels, causing an obstruction to the choroidal blood outflow. The accumulation of fluid may be retained not only in the choroidal tissue but also in the suprachoroidal space. In addition, the presence of LOF may further increase choroidal vascular pressure, choroidal vascular wall stress, and resultant choroidal vascular hyperpermeability.

UES is characterized by idiopathic uveal effusion and typically occurs in nanophthalmos with normal intraocular pressure and no inflammatory findings.[16,17] UES shares some common features with CSC, including a short AL,[8,9] subretinal fluid, choroidal thickening,[12,30] and scleral thickening[18] and is thought to occur owing to inefficient drainage of fluid from the choroidal stroma. This is caused by a thick sclera, insufficient drainage of intraocular fluid from the vortex veins, and reduced scleral permeability.[31] Similar to UES, these pathologic findings may be involved in CSC patients with LOF. Boulanger and as-

sociates[32] reported 3 cases of highly exudative CSC with peripheral choroidal detachment mimicking UES and suggested the role of thick sclera in both entities. Furthermore, several case reports demonstrated the resolution of subretinal fluid using sclerectomy not only in UES[33,34] but also in chronic CSC cases.[35,36] These reports implicate the overlapping pathophysiologic mechanisms between UES and CSC.

This study has several limitations. First, the CSC group mainly consisted of severe cases referred to our university hospital for treatment and did not include mild CSC cases. A variety of CSC cases should be prospectively evaluated in future studies. Second, this study was based on image analysis, and no direct histologic examination was performed. The accumulation of histologic data on the sclera of eyes with CSC is required. Finally, the sclera was measured at the anterior segment, 6 mm from the scleral spur. It was impossible to measure the scleral thickness in the posterior pole. As of this writing, the anatomic features of the sclera surrounding the vortex and posterior poles remain unknown in eyes with CSC. Additionally, further studies are required to investigate how a thick sclera in CSC eyes affects the choroidal structure and circulation.

In conclusion, SCT and scleral thickness were significantly greater in the LOF group than in the non-LOF group in CSC eyes. Moreover, in addition to SCT, scleral thickness was significantly associated with the presence of LOF in CSC. A thick choroid and thick sclera appeared to be independently related to the presence of LOF in CSC. Based on the results, future treatment strategies may target the sclera as a modifiable factor for refractory CSC cases with LOF. For this scope, further studies are required to identify whether and how the sclera influences the pathology of CSC in more detail.

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