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Photoreceptor outer segment layer thinning as a biomarker in acute central serous chorioretinopathy

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Abstract

Background: The photoreceptor outer segment (PROS) layer demonstrates focal thinning above the fluorescein leakage in acute central serous chorioretinopathy (CSC); however, the nature of this phenomenon is not known.

Objectives: To study the relationship between the PROS layer and thickness of the outer retinal layers above the fluorescein leakage in newly diagnosed acute CSC.

Design: Single-center retrospective study.

Methods: All participants received multimodal imaging, including fluorescein angiography and optical coherence tomography. Thickness of PROS, outer nuclear layer (ONL), and ONL-outer plexiform layer (OPL) complex was measured above the leakage and outside the leakage within the area of neurosensory detachment. The number of intraretinal hyperreflective foci of the outer retina was counted. The correlation between PROS thickness and ONL, OPL-ONL complex thickness, and the number of intraretinal hyperreflective foci was calculated.

Results: Fifty eyes of 48 patients (38 males and 10 females, 43.8 ± 10.6 years) with a mean symptom duration of 1.4 ± 1.3 months were included. PROS thickness above the fluorescein leakage showed a statistically significant correlation with ONL thickness, OPL-ONL complex thickness, and the number of hyperreflective foci in the outer retina, 0.57, 0.60, and –0.46, respectively ($p < 0.001$). Measuring the extent of PROS thinning above the leakage in newly diagnosed CSC allowed to predict self-resolution of subretinal fluid. The greatest linear dimension of PROS thinning showed an area under the receiver operating curve (ROC) curve of 0.98. The cases without PROS thinning had the fastest resolution of subretinal fluid.

Conclusion: PROS thinning above the fluorescein leakage in acute CSC is associated with thinning of the outer retinal layers and reveals mild outer retinal atrophy. The absence of PROS thinning predicts faster resolution of CSC.

Keywords: central serous chorioretinopathy, choriocapillaris, hyperreflective foci, optical coherence tomography, photoreceptor outer segment

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Introduction

Changes in the choriocapillaris are considered to play a crucial role in the pathogenesis of central serous chorioretinopathy (CSC). Optical coherence tomography angiography (OCTA) in CSC patients reveals choriocapillaris hypoperfusion in the macula in both affected and fellow eyes in chronic as well as in acute CSC.[1,2] However, the contribution of the choriocapillaris ischemia to the local retinal pigment epithelium (RPE) damage and focal leakage is more challenging to elucidate.[3] Although choriocapillaris flow voids colocalize with choriocapillaris thinning and deep choroidal vessel dilation, RPE abnormalities are

typically present in the leakage area and interfere with the OCT scanning beam, compromising reliable quantification of choriocapillaris loss.[4,5]

From previous studies, we know that the photoreceptor outer segment (PROS) layer is substantially changed in acute CSC and shows focal thinning above the leakage in the acute stage and irregularity in non-resolving cases.[6,7] This local thinning of PROS above the leakage has been explained by washing out of the photoreceptor outer segments by the leakage.[6] However, other mechanisms were not considered in this phenomenon. Choriocapillaris is responsible for supplementation of the outer retina, the status of which may reflect the functional status of the choriocapillaris. Indeed, outer retinal atrophy is an essential part of the clinical picture in chronic CSC and may reflect growing choriocapillaris ischemia, but similar changes are not considered in acute CSC.[8,9]

Here, we theorize that local choriocapillaris ischemia may contribute to the local PROS thinning in acute CSC. If so, other signs of outer retinal atrophy may be found in conjunction with the local PROS thinning, including outer nuclear layer (ONL) thinning or intraretinal hyperreflective foci representing atrophic changes of the retina. This study was, therefore, focused on the relationship between PROS layer thickness and signs of atrophic alteration of the outer retina above the leakage in acute CSC.

Methods

This was a single-center retrospective study that included only newly diagnosed acute CSC cases. The study followed the ethical standards stated in the Declaration of Helsinki and was approved by the Local Ethics Committee of Military Medical Academy (extract from protocol #232 from 18 February 2020) and was conducted from May 2020 to November 2021. Written informed consent was obtained from all participants included in the study.

Exclusion criteria were age more than 60 years, chronic CSC, including CSC cases associated with choroidal neovascularization, posterior cystoid degeneration, gravitational tracks or substantial alteration of RPE or known duration more than 6 months, previous episodes of CSC, ongoing treatment with aldosterone receptors antagonists, and any concurrent ocular condition impeding retinal imaging.

All patients received a comprehensive ophthalmic examination and multimodal imaging, including OCTA (RTVue-XR; Optovue, Fremont, CA) and fluorescein angiography (FA; F-10, NIDEK, Gamagory, Japan). All imaging procedures were performed after mydriasis was achieved by administering topical tropicamide 1%. Electronic medical records were reviewed to analyze the relationships between PROS status and different demographical and clinical characteristics.

The status of the PROS layer and associated structural changes of the neurosensory retina were assessed on structural B-scans extracted from 6-mm OCTA pattern. Each OCTA scan was obtained from averaging two orthogonal scans, consisting of 400 B-scans each of 400 A-scans, which provided high-resolution structural B-scans. In our study, we used OCTA scans as a source of high quality of structural data not for analysis of angiographic information. The leakage was initially detected on FA and was then marked on the structural en face image of OCTA scan. In each case, one to five randomly selected B-scans crossing the leakage area were exported and uploaded in ImageJ software (NIH, Bethesda, PA). To analyze the correlation between PROS and ONL, PROS thickness and ONL thickness were measured at regular intervals 500 μm apart using a line tool. PROS thickness was defined as the distance from the inner border of the ellipsoid layer to the outer border of the neurosensory retina. ONL thickness was defined as the distance from the outer border of the outer plexiform layer to the external limiting membrane. To avoid the influence of the OCT directional changes on ONL measurements, the thickness of the complex of the outer plexiform layer (OPL) and ONL was measured simultaneously with ONL thickness. OPL-ONL complex thickness was defined as the distance from the border between IPL and the inner nuclear layer and the external limiting membrane (Figure 1).

To analyze the correlation between intraretinal hyperreflective foci and PROS thickness, for each scan, the mean PROS thickness over the detached neurosensory retina at each analyzed scan was measured, as well as the number of the intraretinal hyperreflective foci. For each scan, the mean PROS thickness was calculated as a mean value of PROS thickness at regular intervals 500 μm apart over entire neurosensory detachment using a line tool. Therefore in this analysis, all intraretinal hyperreflective foci visible on the scan were

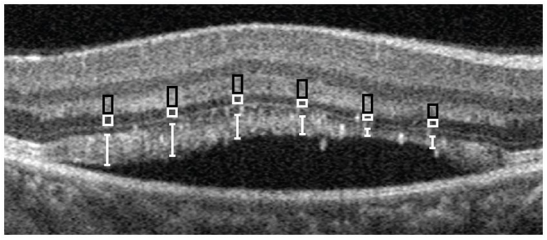

Figure 1. Measurement of outer nuclear layer–outer plexiform layer complex and photoreceptor outer segment layer.
White lines represent photoreceptor outer segment layer thickness, white boxes represent outer nuclear layer thickness, pairs of black and white boxes represent thickness of outer nuclear layer–outer plexiform layer complex.

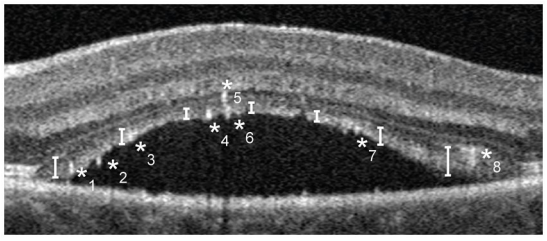

Figure 2. Evaluation of relationship between photoreceptor outer segment layer thickness over entire B-scan and number of intraretinal hyperreflective foci.
White lines represent photoreceptor outer segment layer thickness at evenly distributed points. Asterisks note intraretinal hyperreflective foci.

counted and compared with the mean PROS thickness. The intraretinal hyperreflective foci were defined as any bright dot-like material between the outer border of PROS and OPL without back-shadowing effect (Figure 2).

In addition, the thickness of PROS was measured over selected intraretinal hyperreflective foci and compared with PROS thickness within the area without intraretinal hyperreflective foci. For this analysis, the area without intraretinal hyperreflective foci was selected from within the region of the neurosensory detachment outside the leakage, where the PROS layer was visually unaffected (Figure 3).

To establish if the changes of outer retina above the leakage have a stable character, the thickness of ONL above the leakage was measured after subretinal fluid (SRF) resolution compared with ONL thickness outside the leakage area. To

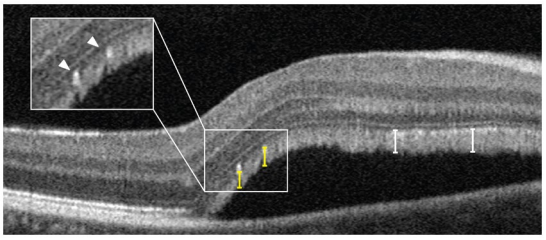

Figure 3. Measurement of photoreceptor outer segment layer at intraretinal hyperreflective foci.
White lines represent photoreceptor outer segment layer thickness. Arrowheads indicate intraretinal hyperreflective foci.

define the ONL thickness above the leakage the mean of three measurements was used. The ONL thickness outside the leakage was defined as the mean of four measurements (two at each side of the leak; Figure 4). In this analysis, the points for measurements within and outside the leakage were chosen by the grader with no fixed intervals between them.

In order to perform an analysis of the prognostic value of PROS thinning for newly diagnosed acute CSC, the greatest linear dimension of PROS thinning was measured on the B-scans above the leakage area (Figure 5). Medical records and OCT data were evaluated to define the outcomes in terms of self-resolution. Cases that resolved after laser treatment (focal laser or microsecond pulsing laser) or the cases which persisted after treatment were defined as persistent. The cases lost to follow-up were excluded.

Statistical analysis was performed with MedCalc 18.4.1 (MedCalc Software, Otend, Belgium). Sample size was calculated by using a power 95% and a significance level of 5%. With a hypothesized correlation coefficient of 0.5 or more, the minimal number of points required for analysis was found to be 46. To find an area under the receiver operating curve (ROC) curve of 0.9 or higher sample size was calculated to be 42 cases or more. The correlation coefficient was calculated between PROS thickness and ONL thickness and the thickness of OPL-ONL complex as well as between mean PROS thickness and the total number of intraretinal hyperreflective foci over the entire B-scan. In addition, the correlation coefficient was calculated between the greatest linear dimension of the PROS thinning of the duration of symptoms and the age of the patients. One-way analysis of variance was used to

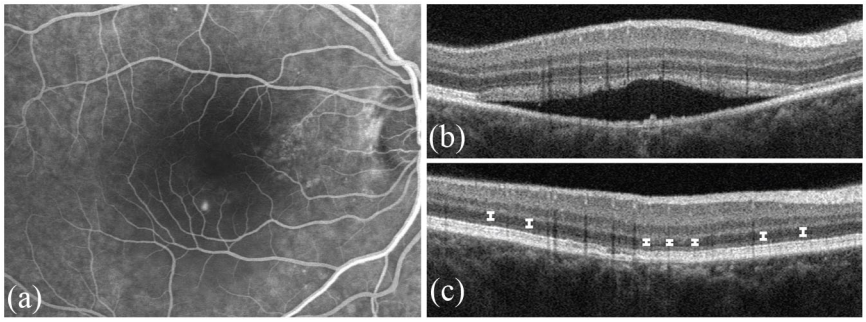

Figure 4. Measurement of outer nuclear layer thickness above former leak. (a) Fluorescein angiography image showing focal leakage at the active phase of the episode. (b) B-scan through the leakage showing photoreceptor outer segment layer thinning at active phase of the episode. (c). B-scan through the leakage showing outer nuclear layer thinning at the active phase of the episode. White lines indicate outer nuclear layer thickness at former leakage and in control regions.

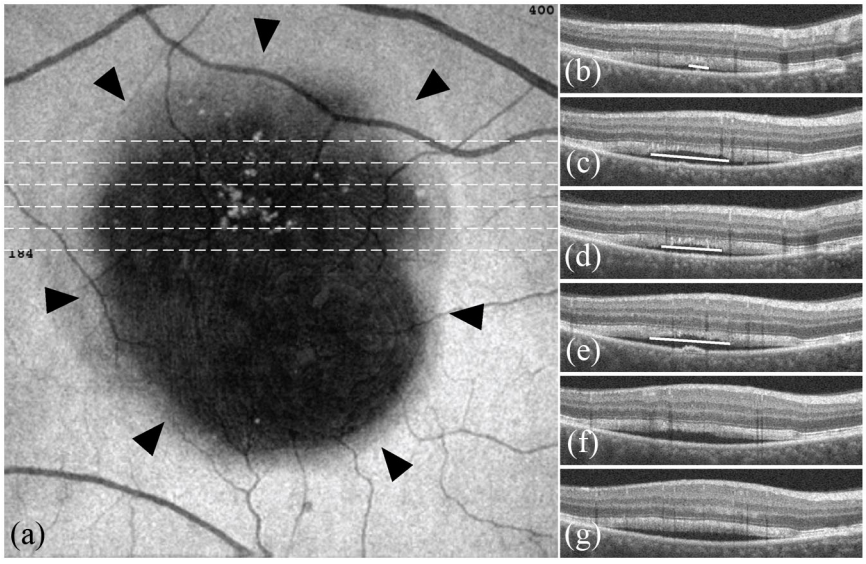

Figure 5. Measurement of the greatest linear dimension of photoreceptor outer segment layer thinning. (a) *En face* structural projection of 6 mm × 6 mm optical coherence tomography angiography scan showing neurosensory detachment (arrowheads). Dashed lines show position of B-scans in b–g. (b–g) B-scans through the area of photoreceptor outer segment layer thinning. White lines show measurements of linear dimension of the area of photoreceptor outer segment layer thinning.

compare demographic and clinical characteristics between eyes with and without PROS thinning. The area under the ROC, sensitivity, and specificity were calculated for the absence of local PROS thinning to discriminate spontaneously resolving CSC cases. To assess the interrater repeatability for calculation of intraretinal hyperreflective foci, the intraclass correlation coefficient was calculated for two graders, who evaluated a subset of 35 B-scans. $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Fifty eyes of 48 patients (38 males and 10 females, 43.8 ± 10.6 years) with a mean symptoms duration of 1.4 ± 1.3 months were included. Six patients reported the use of corticosteroids. The mean best-corrected visual acuity (BCVA) was 0.06 ± 0.09 LogMAR ($\approx$ 20/25 Snellen equivalent). There was no difference in the greatest linear dimension of the PROS thinning between

Table 1. Associations between photoreceptor outer segment layer status (thickness or greatest linear dimension of the thinning) and parameters under study.

	***p* value**
Age	0.32 ($r = -0.15$)
Gender	0.4
Corticosteroids intake	0.38
BCVA	0.88 ($r = 0.02$)
Symptoms duration	0.34 ($r = 0.14$)
ONL thickness	<0.001 ($r = 0.57$)
OPL-ONL complex thickness	<0.001 ($r = 0.6$)
Intraretinal hyperreflective foci	<0.001

BCVA, best-corrected visual acuity; ONL, outer nuclear layer; OPL, outer plexiform layer.

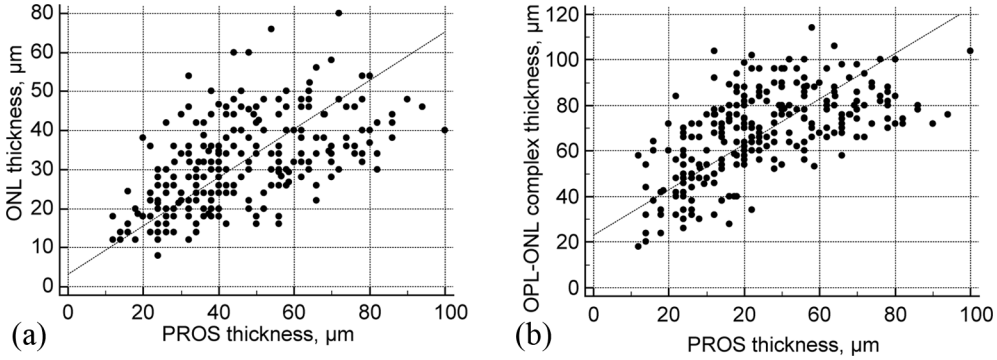

Figure 6. Scattering plots showing correlation of photoreceptor outer segment layer thickness and thickness of outer nuclear layer–outer plexiform layer complex. (a) Correlation between photoreceptor outer segment (PROS) layer thickness and outer nuclear layer (ONL) thickness. (b) Correlation between PROS and outer plexiform layer–outer nuclear layer complex (OPL-ONL) thickness.

males and females (1131 ± 1034 μm and 784 ± 520 μm, respectively, $p = 0.4$) as well as between persons who were taking corticosteroids ($n = 6$) or not (763 ± 572 μm and 1153 ± 1003 μm respectively, $p = 0.38$). One patient who was taking corticosteroids demonstrated spontaneous resolution after discontinuation of corticosteroids, others required treatment. There was no statistically significant correlation between the greatest linear dimension of the PROS thinning and symptoms duration ($r = 0.14$, $p = 0.34$), BCVA ($r = 0.02$, $p = 0.88$), or the age of the patients ($r = -0.15$. $p = 0.32$) (Table 1).

Status of OPL-ONL complex

In total, 248 points from 72 B-scans were analyzed. PROS thickness showed a statistically significant correlation with both ONL and OPL-ONL complex thickness, 0.57 and 0.60, respectively ($p < 0.0001$). The number of intraretinal hyperreflective foci per B-scan was negatively associated with the mean PROS thickness on the B-scan ($r = -0.46$, $p < 0.0001$) (Figure 6). The mean PROS thickness at intraretinal hyperreflective foci was statistically significantly lower compared with that of the areas without intraretinal hyperreflective foci, 34 ± 12 μm and 54 ± 15 μm,

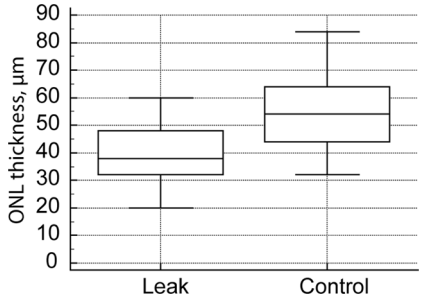

Figure 7. Box-and-whiskers plot showing difference in outer nuclear layer thickness above the former leakage and unaffected regions.
ONL, outer nuclear layer.

respectively ($p < 0.001$) (Table 1). The intraclass correlation coefficient values for identifying intraretinal hyperreflective foci were 0.98 [95% confidence interval (CI): 0.97–0.99].

Status ONL after SRF resolution

Twenty-five treated eyes were included in the analysis of ONL thickness at the leakage after SRF resolution. From those eyes, 18 were treated with focal laser and 7 with microsecond pulsing laser. The mean time after SRF resolution was 1.4 ± 0.8 months. The mean ONL thickness above-resolved leakage after resolution of SRF was statistically significantly lower compared with the ONL thickness in representative control points outside the leakage in the same eye, 39.3 ± 12.1 µm and 55.6 ± 14.3 µm ($p < 0.0001$) (Figure 7).

Prognostic value of PROS thinning

In total, 45 eyes were included in the ROC analysis of the local PROS thinning as a prognostic factor of spontaneous resolution of newly diagnosed CSC cases. Twelve eyes of 12 patients (11 males and 1 female, mean age 42.3 ± 8.1 years) demonstrated spontaneous resolution within a mean time of 2.4 ± 1.8 months after presentation. Twenty eyes (18 patients, 14 males and 4 females, mean age 43.3 ± 10.0 years) were diagnosed as having a recent onset of the disease within a mean period of 0.6 ± 0.4 months before presentation. These patients demonstrated no spontaneous resolution over the next 2 months of observation. Thirteen eyes of 13 patients (10 males and 3 females, mean age 42.8 ± 9.9 years) were diagnosed as having non-resolving CSC based on the previous symptoms duration mean of 3.2 ± 1.0 months. Therefore, in total, 33 eyes were considered as non-resolving based on observation period or symptom duration and were treated. There was no difference in the male-to-female ratio ($p = 0.7$), BCVA ($p = 0.36$), and the age between self-resolved and persistent cases (42.3 ± 8.1 and 43.5 ± 9.8 years, respectively, $p = 0.78$). The greatest linear dimension of PROS thinning in self-resolved and persistent cases was 147 ± 220 and 1373 ± 909 µm, respectively ($p < 0.0001$) (Figure 8). Sensitivity and specificity for the greatest linear dimension of local PROS thinning above the leakage as a predictive biomarker for spontaneous resolution in a newly diagnosed CSC case were 91.7% and 97.2%, respectively, with the area under the ROC curve of 0.98. The cut-off value of the largest PROS thinning linear dimension, which allows identification of cases that resolve spontaneously in a mean period of 2 months, was 319 µm.

Discussion

In this study, we found that local PROS thinning over the fluorescein leakage in newly diagnosed acute CSC is associated with thinning of ONL, OPL-ONL complex, and with the presence of intraretinal hyperreflective foci. PROS thinning may, therefore, be regarded as not just a transient loss or washout of PROS but as a sign of mild outer retinal atrophy. This outer retinal atrophy above the leakage in acute CSC is also confirmed by the presence of persistent ONL thinning after the resolution of subretinal fluid. Here, the mild outer retinal atrophy may be defined as the earliest form of outer retinal atrophy able to be detected with OCT based on local loss of PROS and ONL, and where the PROS thinning is the most notable feature.

PROS thinning is a well-known phenomenon in CSC and is observed in chronic or persistent cases.[8,9] In chronic CSC, the loss of PROS is a part of outer retinal atrophy and is considered to be a result of a long-standing dissociation of RPE and photoreceptors. In chronic CSC, outer retinal atrophy may occupy wide areas of neurosensory detachment and corresponds to the areas of RPE alteration on FA and FAF which in turn correlate to areas of diffuse leakage and neurosensory detachment.[10] Unlike the chronic form, in acute CSC, outer retinal atrophy is not considered to be an essential phenomenon since the duration of the disease is short. However, local PROS thinning has been described in several previous

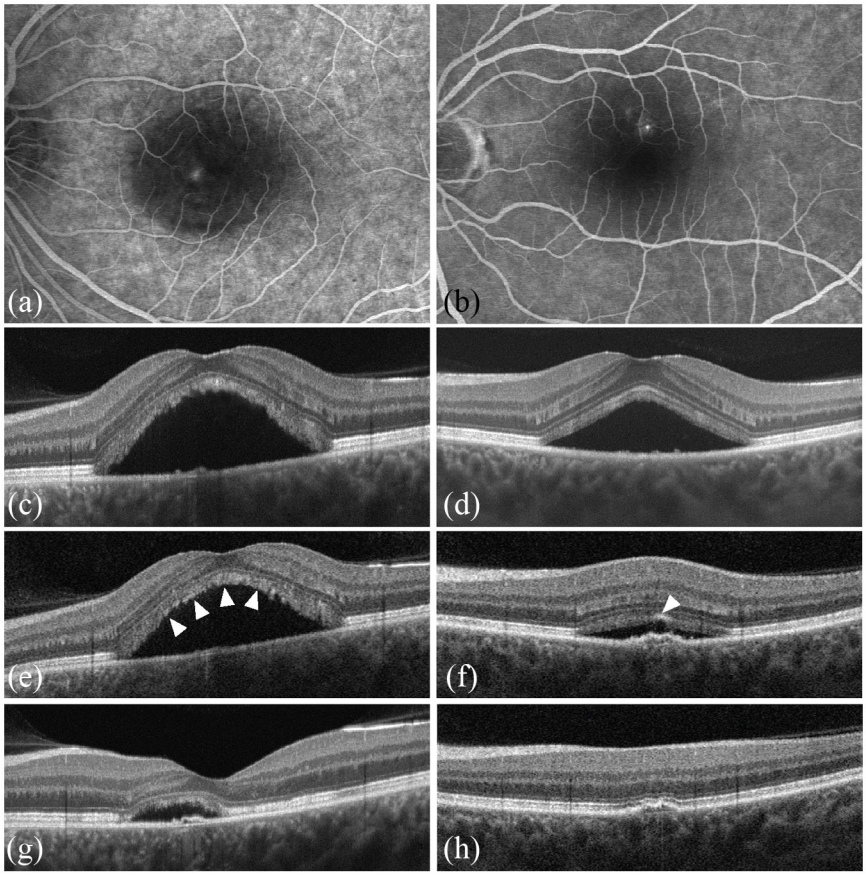

Figure 8. Representative example of outcomes in the acute central serous chorioretinopathy (CSC) cases with different severity of photoreceptor outer segment (PROS) thinning. (a) Fluorescein angiography image showing focal leakage in the case with significant PROS thinning (a. c, e, g). (b) Fluorescein angiography image showing focal leakage in the case with minimal PROS thinning (b, d, f, h). (c) B-scan through the center of the macula in the case with significant PROS thinning. (d) B-scan through the center of the macula in the case with minimal PROS thinning. E. B-scan showing PROS thinning (arrowheads) over relatively wide area (1590 μm). (f) B-scan showing minimal PROS thinning (arrowhead). (g) B-scan at 1 year follow-up examination after two sessions of microsecond pulsing laser therapy. (h) B-scan after 1 month observation period.

studies.[6,7] In contrast to chronic CSC, in acute CSC, it has a local character and appears to be associated with the fluorescein leakage area.[6] In such cases, PROS thinning cannot only be a result of the dissociation of RPE and photoreceptors but has been explained as the result of washing out of outer segments by the leakage flow.[6] However, there are few inconsistencies regarding this explanation. First, clinical observations show that the area of PROS thinning may be larger than the region potentially influenced by the leakage flow which is local in acute CSC. The previous study showed that the linear dimension of an area of PROS thinning may exceed 3000 μm in eyes with a focal fluorescein leak.[6] Second, PROS thinning persists over time despite the intensity of the leakage and the amount of SRF regress within the natural course of the disease. Finally, PROS thinning still exists in eyes without leakage and persistent neurosensory detachment.[11]

The findings of the current study suggest that atrophic changes may contribute to the PROS thinning above the leakage in acute CSC. Indeed, since ONL thinning reflects the irreversible loss of photoreceptors it may result in local PROS thinning. This correlation has been shown in the current study. Moreover, to exclude any potential errors caused by directional artifacts we have analyzed the correlation between PROS and OPL-ONL complex thickness and found a similar association. The correlation between the presence of outer retinal hyperreflective foci and PROS thinning further supports this suggestion.

Intraretinal hyperreflective foci were found to be associated with poor functional outcome in many retinal disorders, including diabetic macular edema,[12] retinal vein occlusions,[12,13] and age-related macular degeneration.[14] In CSC, these hyperreflective foci are also indicative of a negative functional prognosis.[15] Although intraretinal hyperreflective foci may be found at different levels, in CSC they accumulate mostly in the outer retinal layers, including OPL, ONL, PROS, and outer retinal surface. These foci may represent remnants of degraded photoreceptors and reflect outer retinal atrophy. In addition, we found that local ONL thinning may be found above the former leakage area after resolution of subretinal fluid. The most likely cause of atrophic changes in the outer retina above the leakage in acute CSC is local ischemia in the choriocapillaris, which is the only source of nutrients and oxygen to the outer retina. Change in choriocapillaris perfusion is a known biomarker in CSC. An increase in the number of choriocapillaris flow voids in the macula in CSC patients has been demonstrated with OCTA.[1,2,4] A spatial association between choriocapillaris loss and pachyvessels has also been revealed.[16] Although local choriocapillaris ischemia has been put forward as a key cause of RPE alteration, it has not been shown at the leakage site in acute CSC. This may be related to the limitations of OCTA technology in the visualization of the choriocapillaris or to the functional character of the changes in the choriocapillaris which cannot be detected by OCTA. In such cases, PROS thinning, a sign of outer retinal atrophy, may be used as a biomarker for local choriocapillaris ischemia in acute CSC.

The concern could be raised as to whether outer retinal atrophy occurs in acute CSC within a relatively short period of the active phase of the disease. Indeed, local PROS thinning in some cases may be found a few days after the onset of the disease, which is obviously not long enough for outer retinal atrophy to occur. This leads us to suggest that this local outer retinal atrophy is the consequence of the long-standing ischemia existing before the onset of the leakage. Interestingly, for our set of newly diagnosed acute CSC cases, we found only a weak correlation between the duration of symptoms and the severity of the PROS thinning. Since the cases in our study reported no previous episodes of CSC, we may conclude that in acute CSC local PROS thinning above the leakage is defined by factors other than just the episode duration or the recurrence.

In this study, we found that the cases without PROS thinning above the leakage had the highest rate of spontaneous resolution. Since local choriocapillaris ischemia plays a crucial role in the pathogenesis of CSC, its identification may have some prognostic value. Indeed, more severe choriocapillaris ischemia may lead to irreversible RPE damage and persistent leakage, as we see over relatively large areas of the eye fundus in chronic CSC. All of this supports the role of outer retinal atrophy as one of the key and universal biomarkers in CSC. We suggest that intraretinal hyperreflective foci may have a prognostic value similar to PROS layer thinning not least since RPOS thickness and the number of the foci are correlated. It agrees with the previous study, which showed that the baseline number of foci can predict the course of recovery in CSC.[15] However, this suggestion requires additional study because intraretinal hyperreflective foci, unlike the PROS thinning, is not a local phenomenon.

After detachment of neurosensory retina, the PROS elongates due to the lack of phagocytosis by RPE and may mask local thinning in terms of absolute thickness. In other words, the PROS thickness above the leak, even at its thinnest point, may be within normal range, albeit thin compared with other areas outside the leakage where PROS is abnormally thick. The complexity of the PROS changes in CSC required different approaches to be applied in this study to identify subtle outer retinal atrophy, including ONL thickness measurements above the leakage after SRF resolution. Based on these measurements, we conclude that thinning of ONL is indicative of outer retinal atrophy.

This study has several limitations. First, the greatest linear dimension of the PROS thinning does not allow for comprehensive evaluation of the status of PROS layer. To be precisely assessed, loss of the PROS layer requires volumetric measurements and normalization with regard to its mean thickness. However, the advantage of measuring of the greatest linear dimension is the exclusion of the effect of gravitation on the RPOS loss, since the vertical dimension is not taken into account. Second, we cannot completely exclude the effect of laser treatment on the outer retina in the assessment of ONL thickness above the leakage after SRF resolution. However, the correlation of PROS and ONL thickness indicates the presence of outer retinal

atrophy at the same region before treatment. Third, the directional artifacts may substantially affect ONL thickness measurements through a variable display of Henle fibers layer which depends on the height and angle of the detachment. To compensate for this issue, we simultaneously measured the OPL-ONL complex, which as a whole is not affected by the directional artifacts, and which showed a similar correlation with PROS thickness. Since ONL may be responsible for thinning of the entire OPL-ONL complex, and since ONL also demonstrates a correlation with the PROS thinning, we may conclude that ONL and RPOS layer thinning are interrelated.

In conclusion, this study showed that local PROS thinning above the fluorescein leakage in acute CSC is associated with ONL and OPL-ONL complex thinning and intraretinal hyperreflective foci. All of this suggests that PROS thinning above the leakage in acute CSC is a sign of mild outer retinal atrophy, possibly resulting from local choriocapillaris ischemia or disfunction responsible for the leakage. As a structural biomarker of choriocapillaris ischemia, PROS thinning appears to indicate the probability of self-resolution in acute CSC.

Declarations

Ethics approval and consent to participate

The study was approved by the Local Ethics Committee of Military Medical Academy (extract from protocol #232 from 18 February 2020). Written informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Author contributions

Dmitrii S. Maltsev: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

Alexey N. Kulikov: Supervision; Writing – original draft; Writing – review & editing.

Maria A. Burnasheva: Formal analysis; Funding acquisition; Investigation; Visualization; Writing – original draft.

Jay Chhablani: Project administration; Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and material

The data that support the findings of this study are available from the corresponding author (*DSM*) on request.

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