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Optical coherence tomography findings in toxoplasma retinochoroiditis

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Purpose: This study aimed to evaluate the optic coherence tomography (OCT) findings in patients with toxoplasmic retinochoroiditis (TRC). **Methods:** A total of 12 eyes of 12 patients with active TRC were included in the study. At baseline, at the first-month follow-up, at the sixth-month follow-up and at the 1-year follow-up, the TRC lesion OCT and macula OCT were evaluated. **Results:** Hyperreflectivity of the inner retinal layers and an increase in retinal thickness were observed on the OCT examinations of all the patients with an active TRC lesion. The retinal thickness decreased and the reflectivity of retinal layers was disorganized in the OCT images obtained in the follow-up period. Partial posterior hyaloid detachment (PHD) and no PHD were detected in 11 cases and 1 case, respectively. Epiretinal membrane (ERM) had developed in the adjacent region of the scar in 7 patients. With the regression of the lesion, the disruption of the ellipsoid zone (EZ), retinal pigment epithelium (RPE) and external limiting membrane (ELM) improved in the adjacent areas. In all the eyes, ERM and the PHD configuration did progress during the follow-up period. Vitreoschisis was found in 4 of the 11 patients with partial PHD. It was observed that ERM developed in all the patients with vitreoschisis. **Conclusion:** ERM and partial PHD were common in the TRC patients, and there was no progression during the follow-up period. Regeneration of the EZ, RPE and ELM was observed in the follow-up period.

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Toxoplasma retinochoroiditis (TRC) is the most common cause of posterior uveitis in patients who have no immunodeficiency. Although it is associated with a self-limiting chorioretinitis, its complications may cause vision loss.[1,2]

Optical coherence tomography (OCT) studies evaluating active TRC lesions have suggested that migration of inflammatory cells into the vitreous results in spherical deposits on the vitreoretinal interface.[3,4] It has been determined that, in diseases associated with ocular inflammation, these inflammatory cells and immune complexes cause vitreoretinal interface disorders.[5,6] During the active phase of TRC, vitreomacular traction in the vitreoretinal interface, thickened posterior hyaloid adherence and epiretinal membrane (ERM) formation have been reported.[7,8]

Even if inflammation is controlled, uveitis patients with ERM may have decreased visual acuity (VA) and increased ERM thickness in follow-up.[9] In patients with active phase TRC, the long-term effects of vitreoretinal interface disorders on the retinal structure have not been studied before.

Therefore, in this study we aimed to evaluate vitreoretinal interface disorders and the retinal structure in patients diagnosed with TRC based on follow-up OCT examinations.

Methods

Study design

The clinical records of 12 patients diagnosed with an active TRC lesion and admitted to the Retina-Uvea Unit between January 2013 and December 2017 were retrospectively evaluated.

The study was carried out in accordance with the Declaration of Helsinki, and it was approved by the Institutional Ethics Committee (2018/3-17). Written informed consent was obtained from all the participants.

Information about demographics, medical history, concomitant medications, refractive error and OCT examination results were obtained from the patients' medical records. We reviewed the medical records and OCT examinations of all the cases. All of the patients had undergone a standard ocular examination, including a best-corrected visual acuity (BCVA) measurement using Snellen charts, slit-lamp biomicroscopy, dilated biomicroscopic and fundus examination. The BCVA measurements with Snellen charts were converted to logarithm of the minimum angle resolution (LogMAR) visual acuity (VA) for analysis.

The TRC lesions included in the study were located either at the posterior pole or near the arcades. All the patients had experienced symptoms for less than one week and were in the acute phase. The diagnosis of TRC was based on the presence of an active white focal retinal lesion, and it was confirmed by anti-toxoplasma antibody analysis. Patients with other causes of retinitis were excluded. All the patients were treated with oral azithromycin 500 mg/day, sulfamethoxazole 800 mg/trimethoprim 160 mg and prednisone 0.5 mg/kg/day.

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The patients with a chronic systemic disease, ocular or systemic inflammation, previous ophthalmic surgery, retinal pathology, except for TRC, and irregular visits were excluded from the study. Patients with a satellite lesion adjacent to the TRC scar were also excluded from the study.

Study procedures

OCT was performed by the same technician with a spectral-domain (SD)-OCT device (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). The TRC lesion OCT and macula OCT of the patients were evaluated at baseline, and at the first-month, the sixth-month and 1-year follow-ups. The SD-OCT images were generated using the macular raster with 25 B-scans administered over an area of 20 × 15 degrees with each B-scan spaced 242 μm apart.

Cases with poor-quality SD-OCT images that prevented evaluation and quantification of the SD-OCT data were excluded from the study. Data were analysed by two uvea and retina specialists (GT, SKA).

Vitreous opacity, posterior hyaloid detachment (PHD), vitreoschisis, ERM, internal limiting membrane (ILM), inner retinal layer and outer retinal layer structures were evaluated on the OCT images.

The classification criteria of the International Vitreomacular Traction Study Group were used to define these vitreomacular interface pathologies.[9]

ERMs were characterized by hyperreflectivity of the membrane with corrugation along the surface of the internal limiting membrane. Posterior vitreous detachment was evaluated with OCT. The linear signal into the vitreous cavity was considered to be the posterior hyaloid.

The integrity of the retinal layers was evaluated using SD-OCT images. A disruption of the line was diagnosed when there was a loss of each hyperreflective line. Disruption of the outer retinal layers, other than the ellipsoid zone (EZ), could not be measured clearly. Therefore, only a statistical analysis of EZ measurements was performed.

The EZ disruption width was measured one-by-one in all the horizontal scans of the patients in the OCT examination at baseline, and at the first-month, the sixth-month and the 1-year follow-up periods. The average of the EZ disruption measurements on all OCT examinations was calculated. The first-month, sixth-month and 1-year measurements were compared with the acute phase measurement and with each other. The calliper function of the software package was used for data collection.

Statistical analysis

The Statistical Package for the Social Sciences (SSPS, version 17.0, Chicago, Illinois) was used for the statistical analyses. The study data were summarized using descriptive statistics, such as mean and standard deviation (SD), range, frequency, and percentage. The Kolmogorov–Smirnov and the Shapiro–Wilk tests were used to determine the normality of the distribution of the data. The independent samples *t* test and Mann–Whitney test were used to compare the groups for the normal- and nonnormal distributed variables, respectively. We evaluated the intraobserver repeatability using two OCT images obtained by the same operator; interobserver reproducibility was evaluated using two OCT images obtained from two different operators. Mean thickness and intraclass correlation coefficients were calculated to evaluate the repeatability and reproducibility of the thickness. The intraclass correlation coefficient was determined based on a mean rating ($k = 2$), absolute agreement, two-way random-effects model. The intraclass correlation coefficient values that were greater than 0.90 were accepted as excellent reliability. The Mann–Whitney *U* test was used for two independent samples that did not meet the normality test. The Wilcoxon signed-rank test was used to compare two related samples. Statistically significance was defined as a *P* value less than or equal to 0.05.

Results

Of the 12 patients, 5 were female (42%) and 7 were male (58%). The median age of the patients was 25 years (range: 18–42 years). The median follow-up time was 37 months (range: 13–68 months).

The median BCVA was calculated as 0.5 logMAR (range: 1.20–0.20 logMAR) on presentation and 0.075 logMAR (range: 1.0–0.00 logMAR) at the first-year follow-up. There was a statistically significant improvement in BCVA ($P = 0.002$). The clinical findings are summarized in Table 1.

In all patients, there were focal lesions on the posterior pole or near the vascular arcades. None of the lesions were associated with a TRC scar. The fovea was affected in 4 patients.

In all the patients, hyperreflective punctate dots were detected in the preretinal space in the OCT images. Spherical hyperreflective deposition in the vitreous was observed in 1 patient [Fig. 1]. Preretinal hyperreflective dots and spherical deposition were observed to continue in the first month, but they disappeared at the sixth-month follow-up in all cases.

In all the patients, the acute phase OCT examination showed the beginning of hyaloid detachment. In the first-month follow-up, progressive separation and thickening of PHD were observed in 11 patients, but hyaloid adherence was persistent on the TRC scar lesion in these 11 patients. Full expanded detachment of the posterior hyaloid was not seen in any case in the follow-up. In 1 case, although the beginning of hyaloid detachment was seen on the OCT scans at the acute phase, it did not progress [Fig. 1]. In all the cases, there was no change in the follow-up of hyaloid separation at the end of the first month.

ERM developed in the adjacent region of the TRC scar in 7 patients. While the lesion was active, only an intermittent increase in ILM reflectivity was observed. ERM formation was also observed as the activity of the lesion was decreasing and the scar tissue was developing. It was observed that ERM occurred in the continuation of the thickened and adherent partial PHD. None of the patients had ERM in any other areas except for the TRC scar region.

There was no change in the ERM and PHD configuration and structure, deterioration of the retinal layers or traction formation in the follow-up in any of the other patients. Vitreoschisis was found in 4 of the 11 patients with partial PHD [Fig. 2]. It was observed that ERM developed in all the patients with vitreoschisis.

Five patients (42%) had subretinal fluid adjacent to the lesion; of these, 3 patients had a TRC lesion at the fovea. In 2 patients with subfoveal fluid, but no foveal lesion, the subretinal fluid adjacent to the lesion extended to the fovea. In both of these patients, all of the subfoveal retinal layers were regular after the fluid regressed [Figs. 1 and 3]. At the first-month follow-up OCT examination, the subretinal fluid had disappeared.

In all the patients with an active lesion of TRC, the OCT examination showed hyperreflectivity of the inner retinal layers and an increase in retinal thickness. In the active phase, normal configuration of the inner retinal layers was observed in the areas adjacent to the lesion, but disruptions of the outer retinal layers were detected. In the active phase, the median width of the EZ disruption on the horizontal section of the

Table 1: Clinical and laboratory findings of the patients

Patient no	Age/gender	Baseline BCVA (logMAR)	First Year BCVA (logMAR)	IgG/IGM	Vitreous haze
1	21/M	1.10	0.70	+/-	+2
2	19/F	1.00	0.80	+/-	+1
3	38/F	0.70	0.40	+/-	+2
4	20/M	0.40	0.00	+/-	+1
5	19/F	1.20	1.00	+/+	+1
6	23/F	0.40	0.05	+/-	+1
7	30/F	0.30	0.00	+/-	0
8	32/M	0.22	0.05	+/-	+1
9	18/M	0.60	0.10	+/-	0
10	42/F	1.00	0.30	+/+	+1
11	35/M	0.20	0.00	+/-	0
12	27/F	0.30	0.00	+/-	0

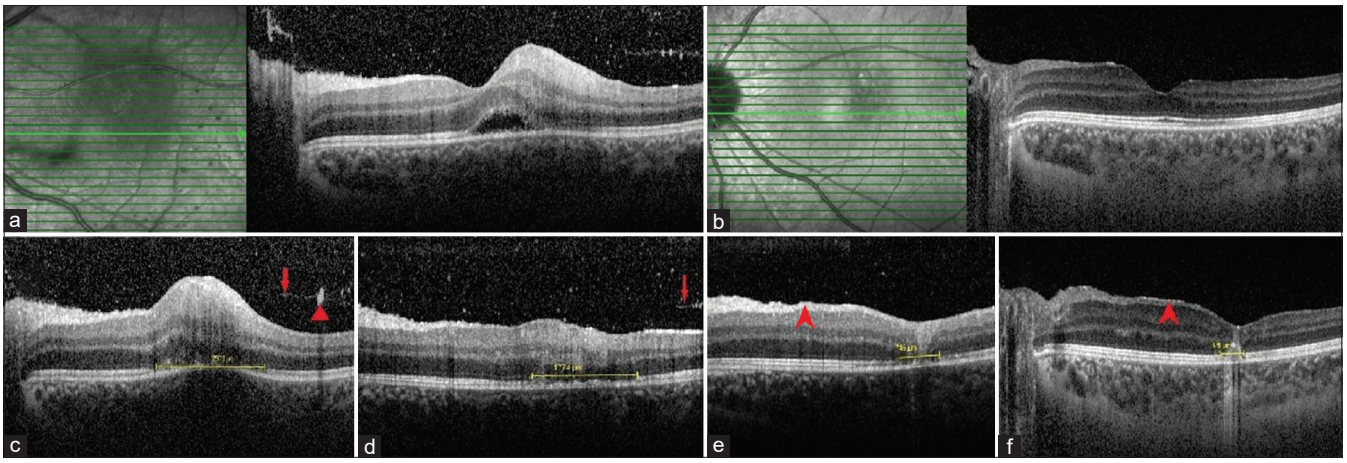

Figure 1: OCT images at baseline (a and c), at the first-month follow-up (d), at the sixth-month follow-up (e) and at the 1-year follow-up (b and f) of a 19-year-old female patient with toxoplasma retinochoroiditis. A-B and C-D-E-F correspond to the same points at follow-up. Subretinal fluid and hyperreflective dots are seen in the fovea (a). The subretinal fluid and hyperreflective dots disappear and all the retinal layers appear to be normal at follow-up (b). Spherical hyperreflective deposition in the vitreous was seen (arrowhead in c). Although the OCT scans showed that hyaloid detachment had begun at baseline and were seen at the first-month follow-up, the posterior hyaloid did not continue to separate and it remained adherent in the follow-up OCT examination. ILM reflectivity is present in the active phase, but ERM (pointed arrow e and f) developed during the follow-up period. Hyperreflectivity of the inner retinal layers, an increase in retinal thickness and disruptions in the outer retinal layers were seen in the active lesion. The retina thickness decreased in the temporal half of the fovea adjacent to the scar (f). The EZ disruption was 2379 μm at baseline (a), 1774 μm at the first-month follow-up (b), 745 μm at the sixth-month follow-up (c) and 515 μm at the 1-year follow-up (d). EZ, RPE and ELM regeneration was seen in the follow-up period

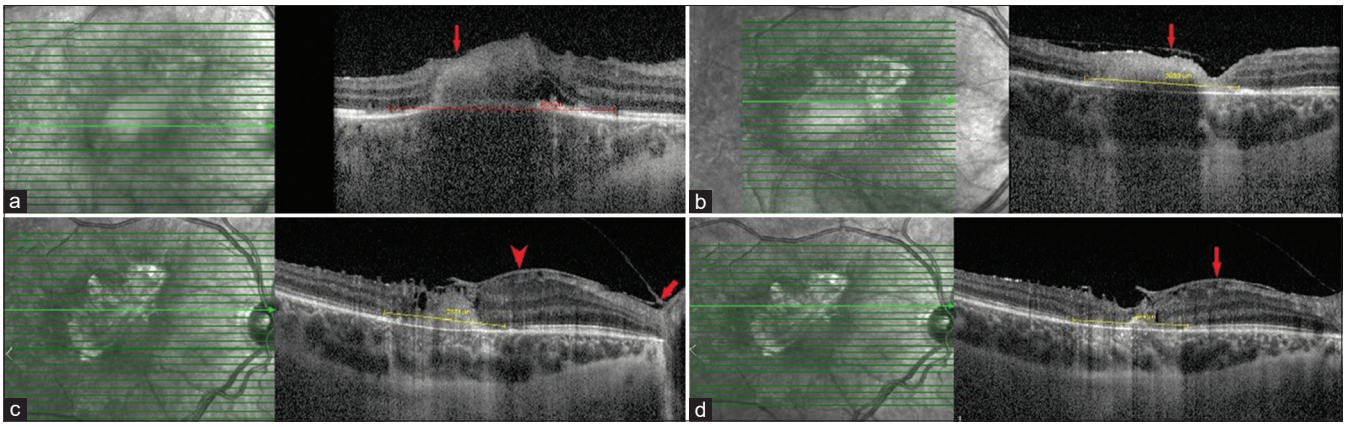

Figure 2: OCT images of a 21-year-old male patient with toxoplasma retinochoroiditis. (a-d) correspond to the same points at follow-up. Hyperreflectivity of the inner retinal layers, an increase in retinal thickness, the presence of subretinal fluid and disruptions in the outer retinal layers were all seen in the active lesion. ILM reflectivity is present in the active phase, but ERM (pointed arrow) and vitreoschisis (arrow) developed during the follow-up period (c and d). The EZ disruption was 4676 μm at baseline (a), 2679 μm at the first-month follow-up (b), 2574 μm at the sixth-month follow-up (c) and 2464 μm at the 1-year follow-up (d). With the regression of the lesion, the pathological appearance of the outer retinal layers improves in these adjacent areas

Table 2: Optic coherence tomography findings

Patient no.	Baseline mean EZ disruption	First-month mean EZ disruption	Sixth-month mean EZ disruption	First-year mean EZ disruption	ERM	Hyaloid detachment/ vitreoschisis	Subretinal fluid
1	4742	3950	2577	2470	+	PHD/+	+
2	2567	1956	1234	1190	+	PHD/-	-
3	2058	1540	1156	980	+	PHD/+	-
4	1200	980	823	800	-	PHD/-	-
5	2379	1774	745	515	-	No HD/-	+*
6	4312	3922	2340	2133	+	PHD/+	+*
7	3250	2670	2330	2147	+	PHD/-	-
8	2764	2215	1436	1380	-	PHD/-	-
9	2882	2234	1987	1832	+	PHD/+	+
10	1788	1430	1234	1173	+	PHD/-	-
11	2768	1890	1233	998	-	PHD/-	-
12	1599	980	786	670	-	PHD/-	+

*Subretinal fluid in the lesion area and extended to the fovea. *EZ: Ellipsoid zone

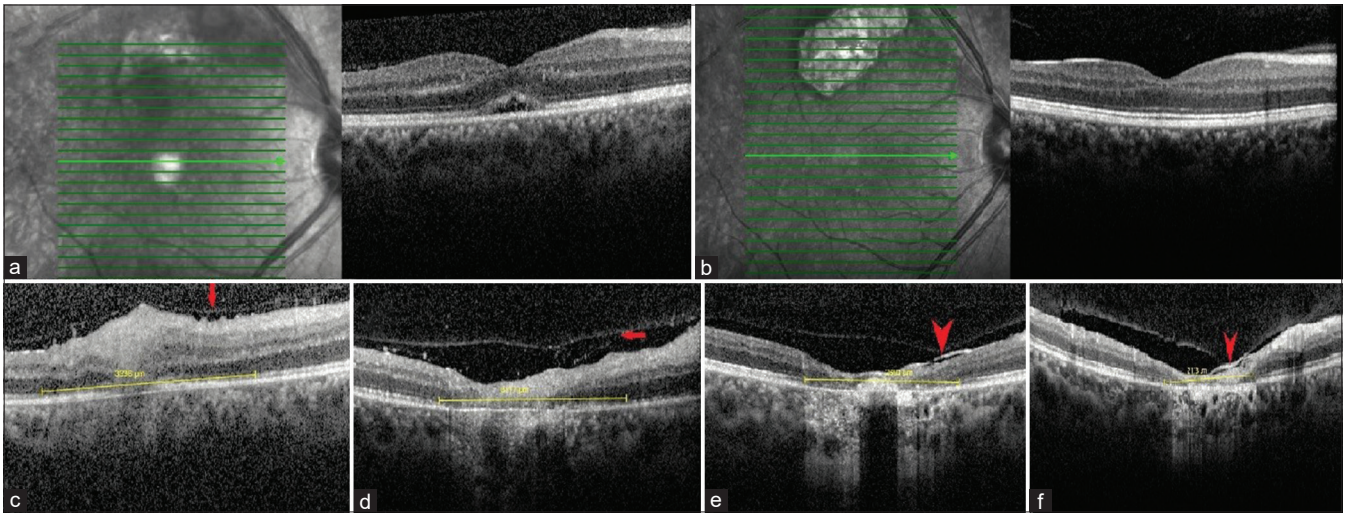

Figure 3: OCT images at baseline (a and c), at the first-month follow-up (d), at the sixth-month follow-up (e) and at the 1-year follow-up (b and f) of a 23-year-old female patient with toxoplasma retinochoroiditis. (a-f) correspond to the same points at follow-up. The subretinal fluid extends to the fovea from the inferior border of active lesion (a). The subretinal fluid and hyperreflective dots disappeared, and all the retinal layers appear to be normal in the follow-up period (b). OCT examination shows that PHD began during the acute phase (c, arrow). Progressive separation of the posterior hyaloid and vitreoschisis (arrow) were seen, but hyaloid adherence was persistent on the TRC scar lesion at the first-month follow-up (d). ERM is seen in e, f; it occurred in the continuation of thickened and adherent partial PHD (arrowhead). Hyperreflectivity of the inner retinal layers, an increase in retinal thickness and disruptions of the outer retinal layers were seen in the active lesion. EZ disruption was 3336 μm at baseline (c), 3117 μm at the first-month follow-up (d), 2690 μm at the sixth-month follow-up (e) and 2133 μm at the 1-year follow-up (f). EZ, RPE and ELM regeneration was seen in the follow-up period

OCT examination was 2565.5 μm (range: 1200–4742 μm). At the first-month follow-up the median EZ disruption was 1923 μm (range: 980–3950 μm), at the sixth-month follow-up it was 1234 μm (range: 745–2577 μm) and at the 1-year follow-up it was 1181.50 μm (range: 515–2470 μm). When the measurements were compared, the EZ disruptions were found to be statistically significantly higher in the acute lesion in comparison to the first-month, the sixth-month and the 1-year measurements ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively).

The first-month measurements were statistically significantly higher than the sixth-month and 1-year measurements ($P < 0.001$, $P < 0.001$, respectively). A statistically significant difference was observed between the 6-month and 1-year measurements ($P < 0.001$). Consequently, although the lesion resulted in scar formation, it was observed that regeneration and healing of the EZ adjacent to the scar continued. With the regression of the lesion, the pathological appearance of the EZ improved in the adjacent areas [Fig. 3]. It was observed that retinal pigment epithelium (RPE) and external limiting membrane (ELM) regeneration accompanied EZ regeneration.

The retinal thickness was decreased, and the reflectivity of the retinal layers was disorganized in the OCT images obtained during the inactive phase of the disease.

The OCT findings are summarized in Table 2. None of the patients had residual vitreous opacity, retinal detachment, persistent macular edema, optic atrophy, choroidal neovascularization or vitreous hemorrhage in the follow-up period.

Discussion

TRC has been shown to cause vitreoretinal interface changes in the lesion site and in the macula.[7,8,10] In this study, we

evaluated the changes in the vitreoretinal interface and in the retinal layers in patients with TRC. We primarily found that ERM and thickened posterior hyaloid configuration, and its effect on the retina, did not progress during the follow-up period. There was no progression of hyaloid separation after the end of the first month.

During follow-up, the EZ adjacent to the scar regenerated. In previous studies, inflammatory granular deposits have been reported in the vitreoretinal interface in patients with acute TRC.[3,4,11] It has been suggested that inflammatory cells and cytokines migrating to this preretinal region cause vitreoretinal interface disorders.[3,4,11] Even if the lesion is not in the macula, these deposits may be present in the preretinal area on the macula in OCT. In the present series, the OCT images obtained in the active phase of TRC showed preretinal hyperreflective dot formations compatible with cell deposits in both the lesion site and the macula. Intraretinal hyperreflective dots were also recorded. Hyperreflective dots that were thought to be inflammatory cells disappeared with treatment.

Although inflammatory cells were seen in the preretinal region, both in the lesion site and the fovea in the active phase, in our study, no macular ERM developed independently of the lesion region. We found that the presence of ERM was connected to partial PHD in the patients. Based on these data, we suggest that the development of ERM in the lesion area arises from posterior hyaloid-related detachment disorders, such as partial PHD and vitreoschisis.

In the follow-up OCT examinations, no changes were observed in the ERM configuration and retinal structure. We believe that this absence of progression was due to the regression of the inflammation. Aleixo *et al*.[11] reported posterior segment problems, such as residual vitreous opacity, retinal detachment, persistent macular edema, optic atrophy, choroidal neovascularization and vitreous hemorrhage, in TRC. We did not record any of these findings in our study.

Orefice *et al*.[8] reported increased posterior hyaloid thickness and spherical hyper-reflective deposits. One of our patients showed spherical hyperreflective deposits. The frequency of subretinal fluid in our study was similar to that reported in another study.[7] The subretinal fluid in the fovea was the continuation of the lesional fluid; therefore, the presence of subfoveal subretinal fluid indicates the importance of the distance between the lesion and the fovea. Regeneration was observed in all the retinal layers of two patients who had no foveal lesion but had subfoveal retinal fluid. In previous studies, RPE fragmentation and retinal layer irregularities were reported in patients with TRC.[7,10] In our study, we observed that the irregularities in the EZ, ELM, and RPE adjacent to the lesion decreased with the regression of the active lesion and inflammation. It was also observed that the disorganization of the retinal layers in the scar region ended sharply and continued with the regular retinal layers in the chronic phase of the disease.

Orefice *et al*. reported a newly developed active lesion adjacent to the old TRC scar in 15 cases.[8] They also found that, although initially there was no pathology at the vitreoretinal interface, posterior hyaloid thickening and partial detachment were detected during follow-up.[8] They observed thickened irregular posterior hyaloid and PHD on the hyperreflective retinal area in patients with active phase TRC.[8] Based on these findings, they suggested that patients with no vitreoretinal interface changes on the scar may have congenital lesions. In our study, there were no findings related to hyaloid detachment in 1 patient. We suggested that the evaluation of hyaloid may provide misleading information about whether or not the TRC lesion is congenital.

Although Diniz *et al*. did not detect ERM in the active phase of TRC, they found that ERM developed adjacent to the scar during the follow-up period.[7] Similarly, in our study, ERM was not detected in the OCT examinations in the active phase of the disease, but ERM development adjacent to the scar was observed in follow-up.

It was reported that ERM progression was slow, and most ERM cases showed no progression for more than 5 years.[12] Therefore, in terms of vitreoretinal interface changes and progression, regular follow-up of these cases is important.

Our study has some limitations. It examined a small number of cases and used a retrospective design. Further prospective studies with a larger number of cases and longer follow-up duration can provide stronger evidence on the causes, risk factors and prognosis of vitreoretinal interface disorders in TRC.

Conclusion

In conclusion, we observed a high rate of ERM in areas adjacent to the TRC scar lesion, and this was found to be related to thickened and adherent partial PHD and vitreoschisis. Vitreoretinal interfacial disorders did not progress during the follow-up period. EZ, RPE and ELM were also seen to be regenerated in the lesion area. Regular OCT examinations are recommended to evaluate retinal layers and vitreoretinal interface disorders in TRC cases.

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Conflict of interest

There are no conflict of interest.

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