Optical coherence tomographic findings of glaucomatous eyes with papillomacular retinoschisis

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Abstract

Objectives

To investigate the topographic relationship between the shape of the optic nerve head (ONH) margin detected by optical coherence tomography (OCT) and the clinical characteristics of papillomacular retinoschisis (PMRS) in glaucomatous eyes.

Methods

The medical record of patients with a PMRS in a glaucomatous eye were reviewed. The eyes were placed into two groups determined by the shape of the ONH margin in the OCT images; eyes with an externally oblique ONH margin (Group 1) and the eyes with an internally oblique ONH margin (Group 2). We compared the clinical characteristics of the PMRS between these two groups.

Results

We studied 31 eyes of 29 patients with PMRS and glaucoma with 24 eyes in Group 1 and 7 eyes in Group 2. The optic nerve fiber layer schisis on the lamina cribosa (LC), beta zone, and gamma zone, and the LC defects were detected significantly more frequently in Group 1 than in Group 2 eyes ($P < 0.05$). A retinal nerve fiber layer schisis was observed around the ONH significantly more frequently in Group 2 than Group 1 eyes ($P < 0.01$).

Conclusion

These findings suggest that the PMRS in Group 1 eyes develops most likely around the LC defects while the PMRS in Group 2 eyes develops most likely from the optic nerve fiber layer around the ONH.

Introduction

A retinoschisis is present in the macular area of eyes with X-linked schisis, pathologic myopia, and optic disc pit maculopathy. $^1$-$^4$ Several single case reports or case series have reported that papillomacular retinoschisis (PMRS) is present in eyes with a glaucomatous optic disc. $^5$-$^{17}$ The pathogenesis for the PRMS associated with glaucoma has not been definitively determined. Based on the findings of fundus fluorescein angiography (FA) and optic coherence tomography (OCT), vitreous fluid or cerebrospinal fluid (CSF) appears to be the source of the fluid in the PMRS although this has also not been definitively determined. $^5$-$^7,^{10,13,17}$ Some research groups have suggested that there is a significant association between vitreous traction or other lateral traction by membranes on the retina and the development of a PMRS. $^{9,12,15}$ This suggestion was made because removing them by vitrectomy improved the PMRS.
There are also some case studies that reported that glaucoma surgery and medications that reduced the intraocular pressure led to an improvement of the PMRS. 6,18

The lamina cribrosa (LC) is a putative site for retinal ganglion cell axonal injury in glaucomatous eyes, 19 and an LC defect is known to be one of the optic nerve head (ONH) changes associated with glaucoma. 20 Some studies have shown that the relationship between a LC defect and PMRS in glaucomatous eyes was based on the OCT findings. 17

The slope of the ONH margin can be classified as an externally oblique margin or an internally oblique margin, 21 and Jong et al. showed that the length of the externally oblique slope was associated with the existences of LC defects in myopic glaucomatous eyes. 22 Other researchers have focused on the obliquity of the ONH margin in glaucomatous eyes, 23,24 but the relationship between the slope of the ONH margin and PMRS including the association with the LC defects has not been determined.

We believe that several mechanisms are involved in the development of PMRS. We suggest that the differences in the obliquity of the ONH margin will affect the development of LC defects and the location where the vitreous or other tractional forces are exerted. This would then affect the source of the fluid in the PMRS. However, we are not aware of any studies that examined the relationship between the obliquity of the ONH margin and the presence of PMRS.

Thus, the purpose of this study was to determine the clinical characteristics and the OCT and FA findings in eyes with PMRS, and to relate them to the obliquity of the ONH margins.

Subjects And Methods

We reviewed the medical records of patients with PMRS associated with glaucoma who were examined in the Eye Center of the Kyorin University from December 2009 to August 2021. All cases were followed for at least 6 months, and the PMRS extended to the fovea in all cases. The procedures used conformed to the tenets of the Declaration of Helsinki, and they were approved by the Institutional Review Board of the Kyorin University School of Medicine (approval number: # 1627).

Glaucoma was diagnosed by the presence of glaucomatous visual field defects, e.g., a nasal step, hemifield defect, generalized depression of the sensitivity of the visual fields, paracentral scotoma, or Bjerrum's scotoma. The ONH morphology, e.g., optic disc rim thinning, optic disc rim notching, diffuse disc excavation, vertical cup-to-disc ratio > 0.7, and/or retinal nerve fiber layer defect was also used to diagnose the glaucoma. All of the glaucoma patients had an open anterior chamber angle by gonioscopy. Highly myopic eyes (refractive error < -8.0 diopters (D) or axial length > 26.5 mm) and eyes with a congenital ONH pit were excluded.

All patients underwent comprehensive ophthalmologic examinations including measurements of the best-corrected visual acuity (BCVA) by a standard Japanese decimal visual acuity chart and the intraocular pressure (IOP). They were also examined by slit-lamp biomicroscopy, indirect
ophthalmoscopy, OCT (OCT Cirrus HD OCT 4000®, Carl Zeiss, Oberkochen, Germany: Spectralis®, Heidelberg Engineering, Heidelberg, Germany: DRI OCT Triton®, Topcon Corporation, Tokyo, Japan), color fundus photography (Vx-10, Vx-20α; KOWA, Nagoya, Japan), and perimetry (Humphrey central 30 – 2 Swedish Interactive Threshold Algorithm standard test; Humphrey-Zeiss Systems, Dublin, CA; Goldman perimetry, INAMI, Tokyo, Japan). A signed written informed consent was obtained for the FA that was recorded with the Spectralis or Vx-10 camera (KOWA, Nagoya, Japan). All patients who wanted were given the medications for glaucoma. Vitrectomy was performed on patients whose BCVA worsened due to a worsening of the PMRS, and who granted permission for the surgery by signing a written informed consent for the surgery. The decimal BCVA was converted to the logarithm of the minimum angle of resolution (log MAR) units for the statistical analyses. The central retinal thickness (CRT) was measured on the OCT images of both eyes.

Strouthidis et al reported that the ONH margin consisted of the border tissue of Elschnig that formed the junction between the scleral surface and Bruch's membrane. Its orientation can be internally oblique or externally oblique as seen in the OCT images. We examined the temporal shape of the ONH margins in eyes with retinoschisis in the OCT images and assigned the eyes into two groups: Group 1 included eyes with an externally oblique margin of the ONH, and Group 2 included eyes with an internally oblique ONH margin. To determine the slope of the ONH margins, we drew a line between the border of Bruch's membrane at the temporal margin of ONH with retinoschisis and a line perpendicular to it. When the ONH margin slope was outside the vertical line, we classified the shape as an externally oblique margin and, when the slope was inside of the line, we classified the shape as internally oblique. We compared the OCT and FA findings between the two group. The existence of vitreous traction was determined by the OCT findings or by the observations during vitrectomy.

**Statistical analyses**

The data are expressed as the means ± standard deviations. The decimal visual acuity was converted to the logarithm of the minimum angle of resolution (log MAR) visual acuity for statistical examinations. The Mann–Whitney U tests were used for unpaired data. The Fisher's exact tests was used for categorical data. Statistical significance was defined as P < 0.05. IBM SPSS statistical software (version 23.0; SPSS Inc., an IBM Company, Chicago, IL, USA) was used for statistical analyses.

**Results**

There were 33 glaucomatous eyes in 31 patients with a PMRS. Two highly myopic eyes were excluded, and in the end, 31 eyes of 29 patients were studied. There were 24 eyes (77.5%) in Group 1 (Fig. 1) and 7 eyes (22.5%) in Group 2 (Fig. 2). Two patients in Group 1 had bilateral retinoschisis. There were 29 eyes with normal tension glaucoma (NTG) and two eyes with primary open angle glaucoma (POAG).

There was no significant difference in the age, initial BCVA, initial IOP, axial length, MD values, sex distribution, glaucoma type, and ONH shape between the two groups (Table 1). One patient rejected
treatment by all topical medications and all others used topical medications to treat their glaucoma. One patient underwent glaucoma surgery with an implantation of an iStent® during cataract surgery. Five eyes in Group 1 and 4 eyes in Group 2 underwent vitrectomy during the experimental period because the BCVA worsened due to the PMRS.

The OCT findings of the retina and ONH are presented in Table 2. There were no significant differences in the percentages of outer nuclear layer schisis, inner nuclear layer schisis, and foveal detachments between the two groups. However, a nerve fiber schisis of the retina was observed significantly more frequently in Group 2 than Group 1 eyes ($P = 0.007$). All eyes in Group 2 had a nerve fiber schisis. The maximum CRT and choroidal thickness under the fovea were not significantly different between the two groups.

A small optic nerve fiber schisis resembling an edema was detected on the LC in the OCT images of the ONH (Fig. 1C, red arrowhead) and on the external oblique margin of the ONH (Fig. 1C, yellow arrowhead). These schises were present significantly more often in Group 1 than in Group 2 eyes ($P < 0.01$, $P < 0.01$). An elevated sponge-like nerve fiber schisis was also detected on the surface of the ONH (Fig. 1B red arrowhead and Fig. 2C red arrowhead) in both groups. The beta zone and gamma zone of the peripapillary atrophic area were also seen significantly more often in Group 1 than in Group 2 eyes ($P = 0.03$, $P < 0.01$). LC defects were observed significantly more frequently in Group 1 than Group 2 eyes (Fig. 1H red arrowhead; $P < 0.01$). One eye in Group 1 had a slit tear of the optic nerve fiber on the ONH and two eyes of Group 2 had a slit tear of the retinal nerve fibers around the ONH and at the edge of ONH (Fig. 2C yellow arrowhead).

There were 12 of 24 eyes with FA data at the first visit in Group 1, and 10 had hyperfluorescent leakage that corresponded with the sponge-like elevated optic nerve fiber schisis in the ONH in all eyes (Figs. 1B-E). An LC defect was detected near the schisis in the OCT images in eight of these eyes. The remaining 2 eyes had no hyperfluorescent lesions and schisis in the ONH. Five of 7 eyes in Group 2 had FA data at the first visit, and none had any hyperfluorescent leakage in the ONH even though 2 eyes had a sponge-like elevated nerve fiber schisis in the ONH as the eyes of Group 1 (Fig. 2C-E). The hyperfluorescent leakage in the ONH in Group 1 began between 26 to 45 seconds after the injection of the fluorescein. The hyperfluorescence did not spread to the retinoschisis. One eye in Group 1 had leakage from the radial papillary capillaries (RPCs) and one eye that had a weak traction between the vessels on the ONH and had leakage from the vessels. The vessels in the deeper layer appeared to be the origin of the hyperfluorescence in the other 8 eyes which did not have leakage from the RPCs and the vessels.

The medical records showed that a Weiss ring was observed by fundus examinations in 17 of 24 eyes in Group 1 and 4 of 7 eyes in Group 2. A residual posterior membrane was observed during vitrectomy in one of 17 eyes with a Weiss ring in Group 1. The medical records of 3 eyes in Group 1 and 1 eye in Group 2 did not mention Weiss ring in the records. In the OCT images, 1 eye of Group 1 had a vitreous traction on the externally oblique disc margin (Fig. 3B) and 1 eye of Group 2 had a vitreous traction on the area of the retinoschisis around the ONH (Fig. 3J, K).
A thin or mottled epiretinal membrane (ERM) was seen around the ONH in 13 of 24 eyes in Group 1 and 2 of 7 eyes in Group 2 in the OCT images. A membrane or some tractional tissue was seen between the vessels or nerve fibers in the ONH in 5 eyes in Group 1 and 2 eyes in Group 2.

The average follow-up duration was 115.8 ± 18.3 months in Group 1 and 121.6 ± 7.0 months in Group 2 (P = 0.872). The average final decimal BCVA was 0.104 ± 0.302 in Group 1 and 0.065 ± 0.224 in Group 2 indicating that there was no significant change between initial and last BCVA in both groups (P = 0.398; P = 0.225).

In the end, the PMRS improved in all 19 eyes of Group 1 without vitrectomy and in 2 of three eyes without vitrectomy in Group 2. Five eyes of Group 1 and 4 eyes of Group 2 underwent vitrectomy. A postoperative macular hole (MH) developed in two of four eyes after the vitrectomy in Group 2 even if one of them had fovea-sparing ILM peeling but in none of five eyes with vitrectomy in Group 1. The PMRS finally improved in the other seven eyes in both groups.

We also examined the fellow eyes. A vitreous traction on the external oblique slope was observed in two eyes with an externally oblique disc margin (Fig. 3E). Another eye with an externally oblique margin had an outer retinal nerve fiber layer schisis and an optic nerve fiber schisis on the LC. In this eye, a vitreous traction was not seen but a membrane was observed on the ONH. One eye with an internally oblique disc margin had a focal nerve fiber retinoschisis around the ONH.

**Discussion**

Our OCT findings showed that an LC defect and a deep optic nerve fiber schisis on the LC were observed significantly more often in Group 1 than in Group 2 eyes. In contrast, retinal nerve fiber schisis around the ONH was observed significantly more frequently in the Group 2 than in Group 1 eyes. These findings suggest that the PMRS in the Group 1 eyes might be associated with the LC defect and extend from deep within the ONH to the retina. On the other hand, the PMRS in Group 2 eyes might develop from the vitreous side around the ONH.

It was recently reported that there was an association between the external oblique changes of the ONH margin and glaucoma (POAG). It was shown that the gamma zone was associated with the absence of glaucoma whereas the beta zone was associated with the presence of glaucoma. The presence of both the beta and gamma zones was correlated with an older age, higher myopia, and larger disc size. Our results showed that the presence of the beta and gamma zones of parapapillary atrophy was observed more frequently in Group 1 eyes. The change of the externally oblique shape and beta and gamma zones may be caused by glaucoma, increasing age, and higher myopia. Thus, the changes in the shapes around ONH may make a difference in the mechanism causing the PMRS including the different sites of vitreous traction and the existence of LC defect in the two groups of eyes.

We reported earlier on the outcomes of vitrectomy on 11 cases of PMRS, and we suggested that vitreous tractional forces may have caused the PMRS. In the present study, many cases already had a posterior
vitreous detachment (PVD) but the OCT findings in some cases showed posterior vitreous traction. In Group 1, the vitreous traction was on the slope of the externally oblique margin of the ONH, but in Group 2, the traction was on the retina around the ONH. The traction on the external slope may have affected the ONH including the LC and LC defect in Group 1 eyes. In Group 2, the vitreous traction on the retina around the ONH may have directly affected the weak retinal nerve fiber interface. Since it takes several months for resolution of PMRS to be completed in cases in which vitrectomy is effective, it is possible that many cases with PVD also have a course of resolution after PVD occurs. We believe that the posterior vitreous traction could cause a retinoschisis, and there may be cases whose PMRS improved after a PVD developed. We need to examine more cases in which the PMRS is developed before the PVD completely develops to make any stronger conclusions.

There have been two suggestions on the source of the retinal fluid located in the schises. The first is that the CSF flows into the retina which is based on the FA finding of hyperfluorescence leakage in the ONH. Also, the OCT findings of the PMRS corresponding to the LC defect in some case reports support this suggestion.\(^{13,16,17}\) The second suggestion is that vitreous fluid flows into the retina through microscopic connections between the ILM and nerve fiber layer. This was based on the absence of any abnormality in the FA findings,\(^{6,7,10}\) and the results of an animal study that showed that ocular hypertension made the ILM pores.\(^{26}\)

Our results showed that 83% of Group 1 eyes had hyperfluorescence corresponding to the elevated sponge-like optic nerve fiber schisis in the ONH. The hyperfluorescence in the majority of these cases appeared to be due to leakage from a deeper layer than the vessels on the ONH. This is supported by the focal fluorescein leakage in the ONH which is similar to that in optic disc pit maculopathy which is known to be associated with the passive gradients that develop between intraocular and extraocular space around the LC defect and vitreous traction.\(^{4,27}\) LC defects were observed significantly more frequently in Group 1 than in Group 2 eyes, and it was recognized in 80% cases with hyperfluorescent leakage in Group 1. It is still not known whether the LC defect allows CFS to flow into the eye as it does in acquired ONH pits.\(^{28}\) It is also not known whether fluorescein can leak into the CSF but it is known that the blood-brain barrier is absent in the circumventricular organs of the brain where fluorescein leakage can occur.\(^{29}\) An animal study showed that fluorescein could be detected in lower concentrations in the CSF than in the blood.\(^{30}\) If the CSF can be stained by fluorescein, the CSF might be the origin of the fluid in the elevated sponge-like optic nerve fiber schisis in the ONH caused by LC defects in Group 1 eyes. However, the hyperfluorescence on the ONH did not spread into the retinoschisis in all eyes. This suggests that the origin of the fluid was not only the CSF but also from the vitreous. A slit tear of the optic nerve fibers on the external slope was observed in one eye of Group 1. The weak nerve fibers around the LC defect in glaucomatous eyes might be moved according to the pressure gradient between the CSF and vitreous fluid. The small tear or micropore of the nerve fiber layer near the LC defect could be an entrance port for the vitreous fluid. The traction of the posterior vitreous cortex may increase the influx of vitreous fluid into the retina via the small tear or micropores. Some studies have reported that medication or surgery for
glaucoma had the effect of improving the PMRS, and they will decrease such a pressure gradient and might be effective in improving the PMRS in our cases.

In Group 2, FA did not show any hyperfluorescence on the ONH, and a nerve fiber retinoschisis was observed in all Group 2 cases. These findings suggest that PMRS could start from vitreous sites around the ONH, and the vitreous fluid might be the source of the schisis fluid in Group 2 eyes. Two eyes showed a slit-like retinal tear around the ONH in Group 2, and this supports this hypothesis.

It was shown that glaucomatous eyes with non-tilted optic disc like the eyes in Group 2 progress more than glaucomatous eyes with a temporal tilted disc. It was suggested that the tilted disc gives rise to an asymmetric increased strain on the nerve fibers, and therefore susceptible axons are damaged. Conversely, the damage in the eyes in Group 2 with a non-tilted disc may be caused by the damage of the weaker retinal nerve fibers. A postoperative MH developed in 2 of 4 eyes in Group 2 and all five eyes in Group 1. The eyes in Group 2 may have a weaker retina than the eyes in Group 1 but more studies are needed.

Previously, various mechanisms were thought to be associated with the PMRS but the indications for treatment are still unknown. If we study more cases with PMRS in the two groups according to the shape of the ONH margin, the correct mechanism may be determined which should then help in selecting the best treatment for PMRS.

There are some limitations in this study. This study was retrospective and all medical records did not have all of the data. In addition, the number of cases was too few to show the mechanism of PMRS decisively. The risk factors for the development of a macular hole must be analyzed in a study of more patients. More long-term observations and multicenter studies may resolve these limitations. We studied cases with complete PMRS, but the analyses of the findings before a PVD occurs will help to provide evidence for the mechanism for the development of a PMRS.

**Declarations**

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**Conflicts of Interest:**

T.I.: Personal fees (lecture fees) from Nikon Co., Ltd., and Santen Pharmaceutical Co., Ltd., outside the submitted work.

Y.K.: Personal fees (lecture fees) from Santen Pharmaceutical Co., Ltd., and Senju Pharmaceutical Co., Ltd., Glaukos, outside the submitted work.,

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Institutional Review Board Statement: This study was approved by the Institutional Review Committee of the Kyorin University School of Medicine (approval number #1627).

Informed Consent Statement: The patients received a detailed explanation of the surgical and ophthalmic procedures, and all signed an informed consent form. The patients consented to our review of their medical records and their anonymized use in medical publications. The patient consent for this study was obtained in an opt-out format.

Data Availability Statement: The data presented in this study are available on request from the first author (T.I.).

References


**Tables**

Tables are available in the Supplementary Files section.
Figure 1

Representative case with a papillomacular retinoschisis (PMRS) in Group 1. The left eye of a 65-year-old man. His best-corrected visual acuity (BCVA) was 0.155 logMAR units at the initial examination.

A through E. Images at the initial examination.
A: Color fundus photograph showing that the optic nerve head (ONH) has a thin rim at the temporal margin and is edematous in the inferotemporal area.

B: Optical coherence tomographic (OCT) image on the first visit. Yellow arrowheads point to a temporal externally oblique margin from Bruch's membrane to the LC in the ONH. A PMRS and a foveal detachment is present. A red arrowhead points to a sponge-like optic nerve fiber schisis in the ONH. The internal limiting membrane (ILM) is separated from optic nerves on the ONH.

C: OCT image of the ONH shows deep optic nerve fiber schisis on the laminar cribrosa (LC; red arrowhead) and on the externally oblique slope (yellow arrowhead).

D: and E: Fluorescein angiographic (FA) images at the first visit. Fluorescein leakage on the inferotemporal area of the ONH begins at 39 second after the injection of the fluorescein. The leakage lesion corresponds to the elevated sponge-like optic nerve fiber schisis on the ONH seen in the OCT image.

F: through J: Images one year after the first visit. The patient was being treated with medications for glaucoma.

F: Color fundus photograph. The edema of the ONH is not present and the rim thinning is more apparent.

G: OCT image shows a resolution of the retinoschisis and foveal detachment.

H: Red arrowhead points to an LC defect in the inferotemporal area of the ONH.

I: Retinal nerve fiber layer (RNFL) map shows the defect in the inferotemporal area.

J: Visual field (Humphrey 30-2) defect corresponding to the RNFL defect.
**Figure 2**

Representative case with PMRS in Group 2. The left eye of a 75-year-old woman. The BCVA at the initial examination was 0.301 log MAR units.

A: through E: Images at the first visit.

A: Color fundus photography. The cupping of ONH is large.
B: OCT image. Yellow arrowheads point to an internally oblique margin of the ONH. A PMRS can be seen in the outer and inner nuclear layers and the nerve fiber layer. A foveal detachment can also be seen.

C: OCT image shows an elevated optic nerve fiber schisis in the ONH (red arrowhead) and the slit tear of the nerve fiber is observed at the edge of the ONH (yellow arrowhead).

D: and E: FA does not show any hyperfluorescent area on the ONH.

F: through I: Images after vitrectomy

F: Color fundus photograph. A rim thinning is observed. Large macula hole developed postoperatively.

G: PMRS is resolved but the macular hole is present.

H: Retinal nerve fiber layer map shows a defect.

I: Visual fields (Humphrey 30-2). A visual field defect corresponding to the rim thinning and RNFL defect can be seen.
Figure 3

Vitreous tractions in eyes with an externally and an internally oblique margin of the ONH.

A-C: An eye of Group 1.

A: Color fundus photograph shows rim thinning.

B: OCT image shows a PMRS and a vitreous traction on the slope of the externally oblique margin of the ONH.
C: Visual fields (Humphrey 30-2) shows a visual field defect corresponding to the site of the rim thinning.

D: through F: Findings in the contralateral eye of an eye in Group 1.

D: Color fundus photograph shows a rim thinning.

E: OCT image shows a vitreous traction on the externally oblique margin of the ONH. There is no retinoschisis.

F: Visual field is almost normal.

G: through K: Eye of Group 2.

G: Color fundus photograph shows rim thinning and retinal nerve fiber layer defect (RNFLD).

H: FA image shows no leakage in the late phase.

I: Visual fields shows a visual field defect corresponding to the RNFLD.

J: and K: OCT image shows the vitreous traction is on the retinoschisis around the ONH.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- table1.xlsx
- table2.xlsx