Paravascular Inner Retinal Defect Associated With High Myopia or Epiretinal Membrane

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IMPORTANCE Paravascular retinal abnormalities are common in highly myopic eyes. However, affected areas may be underestimated, and the pathogenesis and effects on retinal function remain unclear.

OBJECTIVE To prospectively investigate the characteristics and pathogenesis of paravascular inner retinal defects (PIRDs).

DESIGN, SETTING, AND PARTICIPANTS Prospective and observational case series (between April 2013 and April 2014) at a referral retinal practice among 28 patients (41 eyes) with PIRDs. The entire affected retinal area was examined in 4 quadrants in sequential thin sections using optical coherence tomography. The effect of PIRDs on retinal function was examined using Goldmann perimetry.

MAIN OUTCOMES AND MEASURES Morphological changes on optical coherence tomography sections and visual field test by Goldmann perimetry.

RESULTS On fundus photography, PIRDs appeared as spindle-shaped or caterpillar-shaped dark areas along the major retinal vessels disconnected from the optic disc. On optical coherence tomography cross-sections of retinal vessels, PIRDs often appeared as cystoid or fissure-like spaces; however, longitudinal optical coherence tomography sections along retinal vessels revealed that most PIRDs were actually wide defects in the inner retina or located beneath the major retinal vessels, often deviating into the vitreous cavity. Of 41 eyes with PIRDs, 37 (90%) were myopic; 21 eyes (51%) had high myopia. The mean refractive error of the eyes with PIRDs was −7.94 (95% CI, −9.48 to −6.40) diopters. The mean axial length of the eyes with PIRDs was 26.96 (95% CI, 25.42-28.49) mm. Twenty-one eyes (51%) showed epiretinal membrane in the macular area. In these eyes, PIRDs had formed along the temporal arcade vessels, which increasingly deviated toward the fovea by epiretinal membrane traction. Of 41 eyes with PIRDs, 35 showed visual field defects corresponding to the PIRD locations. The most common visual field defects were relative Bjerrum scotoma (in 75% [60 of 80]; 95% CI, 66%-85%) and nasal steps (in 59% [47 of 80]; 95% CI, 48%-70%) corresponding to the PIRD predilection locations.

CONCLUSIONS AND RELEVANCE Paravascular inner retinal defects primarily occur in eyes with high myopia or epiretinal membrane. Deviated retinal vessels due to axial elongation or epiretinal membrane traction may be involved in the pathogenesis. Paravascular inner retinal defects often cause retinal dysfunction corresponding to the location. A PIRD may partially overlap with retinal lesions previously reported as cleavage of the retinal nerve fiber layer, inner retinal cleavage, paravascular retinal cysts, or lamellar holes. However, the term PIRD more precisely describes the characteristic features of the lesion.
A retinal nerve fiber layer defect (NFLD) appears on fundus photography as a darkened, wedge-shaped lesion connected to the optic disc. An NFLD is often accompanied by a corresponding visual field defect and is commonly used as an indicator of glaucoma during diagnosis and management. Chihara and Chihara first reported 3 cases of cleavage of the retinal nerve fiber layer to differentiate it from defect. The authors described this feature in highly myopic eyes to the optic disc and did not have a corresponding visual field defect. The authors described this feature in highly myopic eyes as cleavage of the retinal nerve fiber layer to differentiate it from NFLDs associated with glaucoma. However, that article was published long before optical coherence tomography (OCT) came into common use.

Technological advances in OCT have allowed detailed examination of the retinal architecture, greatly enhancing our understanding of the pathogenesis of various retinal diseases. Using OCT, Komeima et al in 2005 described paravascular inner retinal cleavage in a case report of high myopia, and Hwang et al recently reported a retrospective case series describing inner retinal cleavage in eyes with epiretinal membrane (ERM) and high myopia. In these 2 studies, cleavage of the retinal nerve fiber layer appeared as small empty spaces within the inner retina on OCT cross-sections. Although Komeima et al detected an associated sensitivity reduction using microperimetry, neither study found visual field defects on standard automated perimetry.

We recently encountered patients with high myopia who had spindle-shaped or caterpillar-shaped dark areas along the major retinal vessels that were disconnected from the optic disc on ophthalmoscopy. In these patients, sequential OCT examinations of the retinal vessels showed that the lesions were remarkably widespread, and a broad defect in the paravascular inner retinal tissue was frequently observed. Goldmann perimetry often detected a visual field defect corresponding to the lesion. In the present study, we termed this lesion a paravascular inner retinal defect (PIRD) because it did not appear to be a simple cleavage of the inner retina and was often accompanied by a functional abnormality. The objectives of this study were to prospectively investigate the characteristics and pathogenesis of PIRDs using sequential OCT cross-sections and to evaluate the effect of PIRDs on visual function.

Methods

Study Design

This prospective and observational case series was approved by the ethics committee at Kyoto University Graduate School of Medicine, Kyoto, Japan, and was conducted in accord with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant before any study procedures or examinations were performed.

Included in the study were 41 eyes of 28 participants with PIRDs who were examined at the Department of Ophthalmology and Visual Sciences, Kyoto University Hospital, between April 2013 and April 2014. A PIRD was defined as a defect in the inner retina adjacent to the major retinal vessels that was disconnected from the optic disc on OCT examination. Eyes that met the following criteria were excluded: intraocular pressure exceeding 21 mm Hg; a senile cataract resulting in poor quality OCT images; macular or peripheral chorioretinal atrophy that could cause visual field defects; optic disc abnormalities such as optic disc hypoplasia, superior segmental optic disc hypoplasia, or tilted disc; or previous intraocular surgery, retinal vein occlusion, retinal artery occlusion, diabetic retinopathy, ocular trauma, or glaucoma.

Each patient underwent comprehensive ophthalmic examinations for measuring the best-corrected visual acuity using a Landolt chart, as well as keratometry, refractive error, visual field test by Goldmann perimetry, intraocular pressure using a Goldmann applanation tonometer, and axial length using partial coherence interferometry (IOL-Master; Carl Zeiss Meditec). Testing performed after pupil dilation included fundus biomicroscopy with a noncontact lens, 45° digital fundus photography (3216 × 2136 pixels, TRC-50LX; Topcon Corporation), red-free fundus photography (Heidelberg Retina Angiogram 2; Heidelberg Engineering), and detailed OCT examinations (Spectralis HRA + OCT; Heidelberg Engineering). High myopia was defined as a refractive error (spherical equivalent) of at least −8.0 diopters (D) or an axial length of at least 26.5 mm.

In addition to the ocular evaluation, the patient’s medical record was studied. The presence or absence of diabetes mellitus, systemic hypertension, and dyslipidemia was determined based on diagnosis by a physician or indication of hyperglycemic, hypertension, or dyslipidemia medication use.

OCT Examination of the PIRD Distribution

In each eye, the retinal structure surrounding PIRDs was assessed in detail using Spectralis HRA + OCT at longitudinal sections parallel to and cross-sections vertical to the major retinal vessels. The images were sequentially and thinly imaged in B-scan mode (49 sections of 5°). Each B-scan was the mean of more than 20 scans of a single area. To image all PIRDs, OCT examination was performed in all 4 quadrants.

The 3-dimensional retinal analysis was performed using swept-source OCT (DRI OCT-1; Topcon Corporation). Each scanned area measured 12 × 9 mm², and the retinal images were obtained at multiple points by moving the incorporated internal fixation target, if necessary.

Results

Our study evaluated 41 eyes of 28 participants with PIRDs (8 men and 20 women) 33 to 81 years old (mean [SD] age, 57.4 [13.3] years) (Table). The PIRDs were unilateral in 15 participants and bilateral in 13. The visual acuity ranged from −0.176 to 0.523 logarithm of the minimum angle of resolution (logMAR) (mean [SD], −0.021 [0.175] logMAR); this represents a range of 20/67 to 20/13 in Snellen equivalents. On examination, there were no systemic disorders that seemed to be closely related to PIRDs.
On fundus photography, most PIRDs appeared as spindle-shaped or caterpillar-shaped dark areas along the major retinal vessels and were disconnected from the optic disc (Figures 1, 2, and 3). In contrast to NFLDs associated with glaucoma, most PIRDs had irregular margins, and the widths were variable. The PIRDs were more frequently para-...
venous than para-arterial (eTable in the Supplement). On red-free images, PIRDs appeared as high-contrast retinal rarifications (Figure 1). The PIRDs were more frequently detected in the superior hemisphere and temporal area of the optic disc. In 14 eyes (34%), PIRDs were detected at both the temporal and nasal sides of the optic disc.

On OCT cross-sections of the retinal vessels, PIRDs often appeared as cystoid or fissure-like spaces, with or without the inner retinal surface (Figure 2). However, longitudinal OCT sections along the major retinal vessels revealed that most PIRDs were actually broad defects in the inner retina or retinoschisis-like changes rather than retinal cystoid spaces or lamellar holes (Figures 2 and 3). In the longitudinal sections, PIRDs were located along or beneath the major retinal vessels, often deviating into the vitreous cavity. Longitudinal sections in some eyes with PIRDs showed large defects in the inner retina along the major retinal vessels (Figure 3). All PIRDs were located within the inner retina. However, in one eye with high myopia, a PIRD was accompanied by defects in the outer plexiform layer (eFigure 1 in the Supplement).

Sequential OCT examinations were performed along the major retinal vessels. These showed that the whole PIRD lesions were remarkably large and more widespread than initially apparent on OCT (Figure 3).

Of 41 eyes with PIRDs, 37 (90%) were myopic (Table); 21 eyes (51%) had high myopia. The mean (SD) refractive error of the eyes with PIRDs was −7.94 (5.02) D (range, −18.13 to 1.50 D); the 95% CI for the mean refractive error was −9.48 to −6.40 D. The mean (SD) axial length of the eyes with PIRDs was 26.96 (2.62) mm (range, 22.20-32.73 mm); the 95% CI for the mean axial length was 25.42 to 28.49 mm. Of 41 eyes with PIRDs, 21 (51%) showed ERM in the macular area, and only 6 of 21 eyes exhibited high myopia. In eyes with a normal axial length, sequential examinations revealed that some PIRDs formed along the temporal arcade vessels, which were increasingly deviated toward the fovea by the increased ERM traction (eFigure 2 and eFigure 3 in the Supplement).

The OCT examinations clearly showed an association between the posterior vitreous membrane (PVM) and PIRDs. In the present study, the PVM was sometimes adhered to the retinal surface surrounding PIRDs and seemed to contribute to the opening of the inner PIRD surface (eFigure 4 in the Supplement). However, most PIRDs (91%) had no adhesion of the PVM onto the inner retinal surface. Detailed observation of the longitudinal OCT sections showed that PIRDs occasionally included the serrated retinal component within the inner retina, projecting and connecting to dotted remnants in the inner retinal surface (Figure 2D).

Finally, we assessed visual function in eyes with PIRDs. Of 41 eyes with PIRDs, 35 showed visual field defects corresponding to the PIRD locations (Table). The most common visual field defects were relative scotoma at Bjerrum scotoma and nasal steps corresponding to PIRDs adjacent to the temporal vascular arcades. Bjerrum scotoma and nasal steps were detected in 60 (75%; 95% CI, 66%-85%) and 47 (59%; 95% CI, 48%-70%) of 80 PIRDs that were seen at the temporal side of the optic disc, respectively (Figure 4 and eFigure 3 in the Supplement). In 11 of 35 eyes, the visual field defects were located at the temporal side consistent with PIRDs at the nasal side of the optic disc (Figure 4).
In the present study, we described 41 eyes with PIRDs that showed spindle-shaped or caterpillar-shaped dark areas along the major retinal vessels. Sequential OCT examinations demonstrated that the lesions were widespread and often included a broad defect in the paravascular inner retinal tissue; therefore, we termed this feature a PIRD. Goldmann perimetry often detected a visual field defect corresponding to this lesion. In a histopathological study of eyes with high myopia, Spencer and Foos observed retinal rarefaction around the retinal vessels in the form of paravascular retinal cysts in the inner retina. On histological sections, PIRDs may appear as paravascular retinal cystoid spaces in the inner retina, similar to the OCT cross-sections of PIRDs.

In a previous clinical cohort study, Chihara and Chihara reported 3 cases of cleavage in the retinal nerve fiber layer seen in highly myopic eyes. In their study, cleavage of the retinal nerve fiber layer was spindle-shaped and disconnected from the optic disc. The ophthalmoscopic features appear consistent with PIRDs, but the authors detected no visual field defect corresponding to this feature. In addition, because the authors did not use OCT, the precise pathogenesis was not elucidated.

Using OCT, Ohno-Matsui et al described a case of paravascular retinal cysts associated with high myopia. Subsequently, Shimada et al studied 287 eyes with high myopia and found paravascular retinal cysts in 49.5% and paravascular lamellar holes in 26.8%. In the present study, PIRDs were often identified as cystoid or fissure-like spaces on OCT cross-sections of retinal vessels. In the study by Shimada et al, it is possible that they did not detect the entire lesion within the paravascular inner retina because all OCT was performed vertically or horizontally. In addition, Shimada et al suggested that paravascular lamellar holes form when the inner wall of paravascular retinal cysts is avulsed by vitreous traction. In the present study, the PVM sometimes adhered to the retinal surface around PIRDs and seemed to contribute to the opening of the PIRD inner surface. However, 90 of 98 PIRDs (91%) in our patients had no adhesion of the PVM onto the inner retinal surface. Although some PIRDs seen in our patients may be consistent with the findings by Shimada et al, we speculate that this would not be common.

In a case report of high myopia, Komeima et al observed paravascular inner retinal cleavage examined using OCT. Recently, Hwang et al reported a case series of inner retinal cleavage in eyes with high myopia examined by OCT cross-sections. In these 2 studies, cleavage in the retinal nerve fiber layer was detected as small empty spaces within the inner retina. This feature appears to overlap with PIRDs. However, sequential OCT examinations of the major retinal vessels showed that PIRDs were far larger than indicated on the cross-sections and often appeared as wide paravascular defects in
the inner retina. We believe that the term PIRD indicates the nature of this feature more precisely.

In the patients herein with PIRDs, 18 eyes had high myopia with a long axial length. In eyes with high myopia, Sayanagi et al\(^1\) reported that retinal vascular microfolds were caused by inward traction of the inflexible macular vessels during elongation of the axial length and may be related to the pathogenesis of macular retinoschisis. In the present study, PIRDs occurred most frequently along the retinal arcade vessels. We speculate that anteroposterior elongation of the eyeball in highly myopic eyes causes coaxial deviation of the major retinal vessels, leading to PIRDs along the deviated vessels.

Ripandelli et al\(^2\) reported that cataract surgery increased the risk of retinal detachment in eyes with high myopia. In their study, approximately 20% of cases of retinal detachment in eyes with high myopia originated from small paravascular retinal tears in the posterior pole. The association between paravascular retinal tears and PIRDs remains unclear. Therefore, additional longitudinal studies are necessary to confirm whether PIRDs may progress to full-thickness retinal defects, which eventually lead to retinal detachment.

Recently, Hwang et al\(^3\) reported a retrospective case series of inner retinal cleavage in eyes with ERM. However, the authors did not elucidate whether ERM was a cause or result of cleavage in the inner retina. In the present study, we observed the formation of PIRDs along the temporal arcade vessels that were increasingly deviated toward the fovea by the increased ERM traction. The tractional force induced by ERM could cause retinal vessels to deviate tangentially toward the retinal plane. This may explain why PIRDs induced by macular ERM were observed only at the temporal side of the optic disc.

Epiretinal membrane is a common complication associated with high myopia. Henaine-Berra et al\(^4\) reported that 11.2% of eyes with high myopia exceeding −8 D showed ERM. In the present study, 21 of 41 eyes with PIRDs (51%) had high myopia, while 21 (51%) showed ERM in the macular area. However, of 21 eyes with PIRDs that showed ERM in the macular area, only 6 had high myopia. The ERM traction and elongation of the axial length may be independently involved in the formation of PIRDs.

Recently, Muraoka et al\(^5\) demonstrated that anteroposterior venous tortuosity caused structural changes in the adjacent retinal parenchyma in eyes with retinal vein occlusion. Retinal veins may be more flexible and more easily movable than retinal arteries, which would explain the higher prevalence of PIRDs in the paravenous area. However, it remains unclear why PIRDs were observed more frequently in the superior hemisphere herein. In our study, detailed observation of the OCT sections showed that PIRDs occasionally included a serrated retinal component within the inner retina that projected and connected to the dotted remnant within the inner retinal surface. Moreover, in one eye with high myopia, a PIRD was accompanied by defects in the outer plexiform layer. These findings suggest not only a mechanical cause but also subsequent degenerative changes that may be involved in the development of PIRDs.
On fundus photography, most PIRDs appeared as spindle-shaped or caterpillar-shaped dark areas along the major retinal vessels. In contrast to NFLDs associated with glaucoma, PIRDs had irregular margins and variable widths. In addition, PIRDs were disconnected from the optic disc. Nukada et al\(^1\) reported that the clinical characteristics of OCT sections of NFLDs in glaucomatous eyes included focally abrupt thinning with regular margins in the retinal nerve fiber layer. Lee et al\(^1\) observed peripapillary retinoschisis in glaucomatous eyes as hyporeflective spaces within the inner retina on OCT sections that were attached to the optic disc border. An NFLD and peripapillary retinoschisis in glaucomatous eyes appear to differ distinctly from PIRDs.

In the present study, 35 eyes with PIRDs (85%) showed visual field defects. Komeima et al\(^9\) also demonstrated a corresponding relative scotoma in a case of a paravascular inner retinal cleavage using microperimetry. However, in the other studies reported herein, no visual field defect was detected corresponding to the inner retinal cleavage using standard automated perimetry. Paravascular lesions may not always be stimulated in standard automated perimetry.

The present study has several limitations. First, this study is descriptive and not quantitative and is a case series without control subjects. The prevalence of PIRDs is still unclear. Second, most patients did not undergo long-term follow-up. We could provide only limited information on longitudinal changes of PIRDs over time. Third, our study did not include fluorescein angiography; therefore, retinal vasculitis could not be unequivocally excluded as the cause of PIRDs.

Conclusions
Despite these shortcomings, we described the characteristics and pathogenesis of an inner retinal defect along the major retinal vessels in eyes with high myopia or ERM and termed the lesion a PIRD. In addition, PIRDs caused retinal dysfunction consistent with the lesion location. Based on the present study, PIRDs may not be a rare feature in eyes with high myopia or ERM. Additional prospective cohort studies with longer follow-up periods are necessary to confirm the prevalence of PIRDs, longitudinal changes in the pathogenesis, and associated retinal dysfunction.
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REFERENCES


