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Characteristics of peripapillary detachment in pathologic myopia

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Running title: Characteristics and incidence of peripapillary detachment in pathologic myopia

Abstract

Objective: To evaluate the prevalence and clinical features of a newly recognized peripapillary lesion specific to high myopia, peripapillary detachment in pathologic myopia (PDPM), in a large series of highly myopic patients.

Methods: Three hundred and twenty-four patients (632 eyes) with high myopia were enrolled in this study. The prevalence, range, fluorescein and indocyanine green angiographic findings, and optical coherent tomography (OCT) findings of PDPM were examined in these patients. Visual field testing (Goldmann kinetic perimetry and Humphrey 30-2 program) was also performed in the patients with PDPM.

Results: PDPM was identified in 31 of 632 highly myopic eyes (4.9%). The OCT scan across the PDPM lesion revealed a localized detachment of retinal pigment epithelium adjacent to the optic nerve. Although PDPM was always situated adjacent to the inferior edge of the optic disc, in some patients it surrounded almost the entire optic disc. There was a steep excavation of the inferior myopic conus adjacent to the PDPM, and the inferotemporal retinal vein was markedly bent at the transition from the PDPM to the excavated myopic conus. Glaucomatous visual field defects were frequently detected in eyes with PDPM (71.0%).

Conclusions: The findings of this study indicate that PDPM is not uncommon among highly myopic eyes. Although its pathogenesis and pathologic significance require further classification,

PDPM might be another indicator of visual field defects in high myopia.

Introduction

In many developed countries, a major cause of legal blindness is high myopia.[1-3] In the United States, the prevalence of high myopia with a refractive error greater than -7.9 diopters ranges from 0.2% to 0.4% .[2] In Asia and the Middle East, high myopia is particularly common.[4] In Japan, the number of cases of myopia is unknown, but pathologic or high myopia is estimated to affect 6 to 18% of the myopic population, and approximately 1% of the general population.[5]

In highly myopic eyes, axial length elongation induces changes in the posterior fundus, including the optic disc.[6] Typical changes of the myopic disc include tilting with the temporal side flattened, and elevation of the nasal side with the edge raised. In addition, a concentric area of depigmentation, known as the myopic conus or temporal crescent, often surrounds the optic disc.

In 2003, Freund et al.[7] reported a newly recognized lesion around the optic disc in highly myopic eyes, termed peripapillary detachment in pathologic myopia (PDPM). They reported that PDPM is observed as an elevated, well-circumscribed, dome-shaped, yellow-orange lesion inferior to the optic disc along the inferior margin of the myopic conus by ophthalmoscopic examination. Ophthalmic coherence tomography (OCT) demonstrated a localized detachment of the retinal pigment epithelium (RPE) and retina corresponding to the PDPM in each of the 20 eyes of 15 patients examined. There was no apparent negative effect on visual function in their patients.

The clinical features, however, including the prevalence, pathogenesis, and clinical

significance of PDPM, remain unclear. In the present study, we evaluated the prevalence and clinical features of PDPM in a large series of highly myopic patients to clarify the pathogenesis and clinical significance of this newly recognized peripapillary lesion.

Patients and Methods

The study was performed according to the guidelines of the Declaration of Helsinki, after obtaining informed consent. The study protocol was approved by the Ethics Committee of the Tokyo Medical and Dental University, Tokyo, Japan. Three hundred and twenty-four patients (632 eyes) with high myopia were identified using clinical records from 1988 to 2003 at the high myopia clinic at the Tokyo Medical and Dental University and enrolled in this study. The inclusion criteria were: (1) refractive error of -8 diopters (D) or more; and (2) fundus changes typical of pathologic myopia: chorioretinal atrophy, lacquer cracks, and atrophic patches. Exclusion criteria included a history of retinal detachment surgery and ocular injuries. There were 109 men and 215 women with a mean age of 49.0 ± 16.8 years (range, 7 - 85 years). The mean refractive error was -12.9 ± 4.60 D (range, -8.25 to -27.0D). The mean axial length was 28.2 ± 1.30 mm (range, 25.9 - 33.3 mm). Each patient underwent a complete ophthalmologic examination, including best-corrected visual acuity measurement, intraocular pressure (IOP) measurement, anterior segment biomicroscopy, visual field testing, and dilated fundus examination using stereoscopic observation. Color fundus photographs were obtained from all patients. Using color fundus

photographs, eyes with a yellow-orange lesion inferior to the optic disc suggestive of PDPM were identified.

Then, the eyes with yellow-orange lesion were prospectively examined in detail. To confirm RPE detachment, OCT was performed in the eyes with a yellow-orange lesion inferior to the optic disc as described by Freund et al.[7] Using a commercially available OCT machine (OCT 2000 scanner, Zeiss-Humphrey, San Leandro, CA). The OCT images were generated using 6-mm radial scans in a spokelike pattern according to the manufacturer's protocol. The OCT operator closely monitored patient fixation under direct visualization, and scanning was repeated until all reasonable attempts had been made to obtain excellent fixation maintained over the entire 1.92 seconds.

In each eye for which OCT confirmed PDPM, the range of PDPM was determined both ophthalmoscopically as well as by OCT. The range of PDPM was categorized into three groups: Grade 1, PDPM formed less than a semicircle around the optic disc or myopic conus; Grade 2, PDPM formed more than a semicircle around the optic disc or myopic conus, but less than 3/4 around the optic disc or myopic conus; Grade 3, PDPM surrounded more than 3/4 of the optic disc or myopic conus.

Fluorescein fundus angiography was performed in all the patients with PDPM using a Topcon TRC-50 IA fundus camera (Topcon, Tokyo, Japan) after injection of 4 ml of sodium

fluorescein into the cubital vein. Indocyanine green (ICG) angiography was also performed with a Topcon TRC-50IA fundus camera in patients who agreed to the examination. For the ICG procedure, 50 mg of ICG (Ophthagreen, Santen Pharmaceutical, Tokyo, Japan) dissolved in 5 ml of distilled solution was injected into the cubital vein. Informed consent was obtained from all patients before performing angiography.

Visual field testing (Goldmann kinetic perimetry) was also performed. Visual fields were examined after complete correction of refraction anomalies using disposable soft contact lenses. Field defects were detected by Goldmann perimetry, and glaucomatous visual field loss was examined. Glaucomatous visual field loss included at least one of the following defects: nasal step, arcuate scotoma, double arcuate scotomas, generalized constriction relative to the fellow eye, or temporal wedge, which could not be explained by myopic fundus changes. Humphrey Visual Field Analyzer (Zeiss Humphrey Systems, Dublin, CA) C30-2 program with good reliability (fixation loss <20%, false-negative or false-positive responses <33%) was also performed in subjects who agreed to the examination. Abnormal Humphrey 30-2 Glaucoma Hemifield Test included one or more of the following defects that were not explained by myopic fundus changes: (1) arcuate or paracentral scotoma, at least four contiguous points on the pattern deviation plot depressed at the P < 0.005 level; (2) nasal step at least two horizontal points in width (10 degrees) on the pattern deviation plot depressed at P < 0.005 level; or (3) advanced glaucomatous field loss.[8] Changes in

the PDPM area were retrospectively examined in the cases for which a series of fundus photographs had been taken before the enrollment to the present study.

Results

PDPM was ophthalmoscopically identified in 31 of 632 eyes (4.9%). Table 1 shows the clinical data of these 31 eyes (23 patients: 13 men, 10 women; mean age: 57.7 ± 14.3 years, range 39 - 78 years). The mean refractive error in eyes with PDPM was -11.4 ± 3.53 D (range -8.25 to -21.0 D), and the mean axial length was 27.7 ± 1.42 mm (range 25.3 - 30.1 mm). The mean logarithm of the minimum angle of resolution (logMAR) was 0.59 ± 0.34 (range 0 – 1.52). Five patients had macular choroidal neovascularization caused by pathologic myopia. Tilted optic discs were observed in 29 of 31 eyes (93.5%), and posterior staphyloma was detected in 19 of 31 eyes (61.3 %) by stereoscopic observation. A peripapillary crescent (myopic conus) was observed in all eyes with PDPM. The distribution of patients' ages among highly myopic patients with PDPM and without PDPM is shown in Figure 1. PDPM was never observed in patients younger than age 30. Figures 2 and 3 show the distribution of the refractive error and axial length in highly myopic eyes with and without PDPM, respectively. Although PDPM was mainly observed in eyes with a relatively mild refractive error or short axial length within highly myopic patients, there was no obvious trend.

In all the patients with ophthalmoscopically detected PDPM, the OCT scan across the

PDPM lesion revealed what appeared to be a localized detachment adjacent to the optic nerve (Figures 4 - 7). In all the patients, fluid appeared to be beneath both the neurosensory retina and the RPE. In three patients, OCT revealed an apparent discontinuity or cleft in the retinal layers at the point of transition from the PDPM to the myopic conus (Figures 6B, 7E).

Regarding the range of PDPM, 20 of 31 eyes (64.5%) had Grade 1 involvement, 7 eyes (22.6%) had Grade 2 involvement, and 4 eyes (12.9%) had Grade 3 involvement. Regardless of the range of the lesion, PDPM consistently included the area inferior to the optic disc in all patients. There was a deep and steep excavation of the inferior myopic conus adjacent to the PDPM in 26 of 31 eyes (83.9%) by stereoscopic observation using +90 D lenses. In these 26 eyes with steep excavation of the myopic conus, the inferotemporal retinal vein markedly bent at the transition from the PDPM to the myopic conus (Figures 4B). Moreover, in seven patients with extreme excavation of the myopic conus, the inferotemporal retinal vein appeared to enter into the PDPM space after bending at the border between the myopic conus and PDPM (Figures 5A), or even disappear at the border of the myopic conus and PDPM in six patients (Figure 7A).

Fluorescein fundus angiography was performed in all patients with PDPM. In most patients (20 of 23 patients), the fluorescein angiogram showed early hypofluorescence and late hyperfluorescence in the PDPM area (Figures 4, 5). In three patients, however, fluorescein angiograms consistently revealed mild hypofluorescence in the PDPM area. There was no early

hyperfluorescence typical of serous pigment epithelial detachments, or leakage suggestive of active choroidal neovascularization. ICG angiogram revealed hypofluorescence in the area of PDPM (Figures 5, 7) in all 15 patients who agreed for the examination. ICG angiogram also demonstrated a markedly bent inferotemporal retinal vein at the border between the myopic conus and PDPM, which eventually refluxed into the center of the optic disc (Figure 5E).

Goldmann visual field examination was performed in all highly myopic eyes with PDPM and in 564 of 601 eyes without PDPM. Among 31 eyes with PDPM, a characteristic glaucomatous visual field defect was detected in 22 eyes (71.0%). A Humphrey visual field analyzer was used in 15 of these 22 eyes and confirmed the visual field defects in all the eyes examined. The IOP of these 22 eyes was 13.2 mmHg ± 3.5 mmHg (range 10~22). Of 22 eyes, 18 received glaucomatous medical treatments. On the other hand, among 564 eyes without PDPM, a characteristic glaucomatous visual field defect was detected in 130 eyes (23.0%). There was a significant difference in the incidence of glaucomatous visual field defect between the eyes with PDPM and without PDPM (Fisher's exact probability test, $P<0.05$).

Thirty-one eyes with PDPM had had a history of periodical examination of average 7.3 ± 3.5 years (0.5 to 13 years) before the enrollment to the present study. There were no changes noted in the size of the PDPM by retrospective review of serial photographs in any of these patients.

Cases

Case 1

A 60-year-old man was examined for high myopia in both eyes. His best-corrected visual acuity was 0.7 OD and 0.6 OS. The refractive error was -13.0 D in the right eye and -15.0 D in the left, and the axial length measurements were 27.4 in the right eye and 28.2 mm in the left. The right eye had a tilted disc with a peripapillary myopic conus. The right eye had a yellow inferonasal peripapillary elevated lesion at the inferior edge, clearly distinct from the myopic conus (Figure 4A, 4B). There was a deep excavation in the inferior part of myopic conus. Abnormal retinal vasculature was observed; the inferotemporal retinal vein was markedly bent at the border edge between the myopic conus and the PDPM (Figure 4B, arrowhead). A fluorescein angiogram of the right eye revealed initial hypofluorescence and late hyperfluorescence of the PDPM area (Figure 4C, D). OCT revealed a nonreflective area that appeared to be beneath the RPE and retina corresponding to the area of PDPM (Figure 4E, along the arrow in Figure 4B). Goldmann kinetic perimetry using revealed an arcuate scotoma and a nasal step, which were not explained by myopic fundus changes (Figure 4F). Magnetic resonance imaging did not detect any intracranial lesions. The IOP was 12 mmHg in both eyes. The patient was prescribed anti-glaucomatous eye drops and has been followed-up.

Case 2

A 68-year-old man was examined for high myopia in both eyes. He suffered from myopic choroidal neovascularization in the left eye. His best-corrected visual acuity was 0.9 OD and 0.1 OS. The refractive error was -10.0 D in both eyes, and the axial length measurements were 28.4 in the right eye and 28.0 mm in the left. The left eye had a yellow peripapillary elevated lesion that surrounded almost the entire optic disc, and was clearly distinct from the myopic conus (Figure 5A, arrowhead). There was a deep excavation in the inferior part of the myopic conus, and the inferotemporal retinal vein was strongly bent at the border of the myopic conus and PDPM (Figure 5A, arrow). The bent retinal vein appeared to enter into the PDPM space after bending. OCT showed a nonreflective area that appeared to be beneath both the RPE and retina corresponding to the PDPM area (Figure 5B; along the white arrow in Figure 5A). A fluorescein angiogram of the left eye revealed early hypofluorescence and late hyperfluorescence at the PDPM area (Figure 5C, D). ICG angiography also demonstrated mild hypofluorescence at the PDPM area (Figure 5F). ICG angiography demonstrated that the inferotemporal retinal vein enters into the PDPM space (arrowhead) and eventually flows back into the center of the optic disc (Figure 5E).

Case 3

A 48-year-old man was examined for high myopia in both eyes. His best-corrected visual acuity was 1.2 OD and 1.2 OS. The refractive error was -12.0 D in the right eye and -12.0 D in the left, and the axial length measurements were 27.7 in the right eye and 27.5 mm in the left. The right

eye had a yellow inferonasal peripapillary elevated lesion at the inferior edge of the optic disc (Figure 6A, arrowheads). OCT showed a nonreflective area that appeared to be beneath both the RPE and retina corresponding to the PDPM area (Figure 6B, along the arrow in Figure 6A). An OCT scan through the PDPM and the myopic conus revealed what appeared to be a full-thickness defect in the retina-RPE layers (Figure 6B, arrow). Goldmann kinetic perimetry using the V-4, I-4e, and I-2e isopters revealed a nasal step and arcuate scotomas, which were not explained by the myopic fundus change (Figure 6C). Humphrey C30-2 program also demonstrated arcuate scotomas and a nasal step (Figure 6D). MRI did not detect any intracranial lesions in this patient. The IOP was 12 mmHg in both eyes. The patient was prescribed anti-glaucomatous eye drops and was followed-up.

Case 4

A 53-year-old man was examined for high myopia in both eyes. His best-corrected visual acuity was 0.8 OD and 1.0 OS. The refractive error was -9.5 D in the right eye and -8.75 D in the left, and the axial length measurements were 27.0 in the right eye and 26.9 mm in the left. The right eye had a yellow peripapillary elevated lesion mainly situated superotemporal to the optic disc in addition to a small lesion inferior to the optic disc (Figure 7A). OCT showed a nonreflective area that appeared to be beneath both the RPE and retina corresponding to the PDPM area (Figure 7E, along the black arrow in Figure 7A). An OCT scan through the PDPM and the myopic conus

revealed what appeared to be a full-thickness defect in the retina-RPE layers (Figure 7E, arrow). There was a deep excavation of the myopic conus, and the optic disc was difficult to observe because of marked tilting and excavation (Figure 7A). The inferior retinal veins seemed to disappear at the edge of the inferior myopic conus (Figure 7A, white arrow). Goldmann kinetic perimetry using the V-4 and I-4e isopters revealed a nasal step and arcuate scotomas, which were not explained by myopic fundus change (Figure 7B). ICG angiograms demonstrated consistent hypofluorescence at the PDPM area (Figure 7C, D). MRI did not detect any intracranial lesions. The IOP was 10 mmHg in both eyes. The patient was prescribed anti-glaucomatous eye drops and was followed-up.

Comment

In the present study, PDPM was identified in 4.9% of highly myopic eyes (31/632 eyes). Although this is the prevalence among highly myopic patients who were followed - up in our university clinic, the clinical characteristics (patient age, refractive error, and axial length) of the subject population ranged widely and are therefore likely to be representative of a larger population.

Many of the findings of the present study differed from those of Freund et al.[7] First, PDPM was not always confined to the inferior edge of the optic disc in our study. Although PDPM was always situated adjacent to the inferior edge of the optic disc, PDPM surrounded almost the

entire optic disc in some patients, and moreover, PDPM was predominantly located superotemporal to the optic disc in one patient (Case 4). Second, abnormalities of retinal vasculature were frequently detected (83.9% of eyes with PDPM) in our study. The inferotemporal retinal vein was markedly bent at the border edge between the myopic conus and PDPM. In some patients with extreme excavation of the myopic conus, this inferotemporal retinal vein appeared to enter the PDPM space after bending at the border between the myopic conus and the PDPM (Figures 5A), or even disappear at the border of the myopic conus and the PDPM (Figure 7A). Freund et al.[7] also observed anomalous vasculature in one patient, with an inferotemporal vein that appeared to be emanating from the peripapillary RPE lesion, rather than from the optic disc. In our study, ICG angiography clearly delineated that this bent retinal vein eventually refluxed into the center of the optic disc (Figure 5). In eyes with deep and steep excavation of the myopic conus, the peripapillary neurosensory retina as well as the retinal vein might be extensively stretched and folded into the PDPM space. This study suggested that the bent retinal vein at the border between the myopic conus and PDPM was a common phenomenon in patients with PDPM, although whether marked bending of the retinal vein eventually impairs retinal venous flow is uncertain.

The pathogenesis of PDPM is not clear. Freund et al.[7] suggested that PDPM is an incomplete form of choroidal coloboma, because of the consistent inferior location to the optic nerve in their study. The more widespread distribution of PDPM around the optic disc in our

patients suggests that this possibility is unlikely. Also, PDPM was never noted in patients younger than 30 years of age, which suggests that PDPM develops later with age and might not be a congenital lesion. Freund et al.[7] also suggested that PDPM represents the gravitation of subretinal fluid originating from the area of the optic disc or optic pits. In our study, an OCT scan of the edge of the lesion demonstrated an absence of all the retinal layers at the margin of the PDPM in three patients. Although it is unclear whether the cleft demonstrated by OCT reflects a true defect in the retina histopathologically, it is possible that vitreous fluid penetrated into the subretinal space through a defect in the retinal layers at the inferior margin of the myopic conus in the area within the very atrophic retina. If the hypothesis of Freund et al.[7] is correct, then it is more probable that the PDPM represents a neurosensory retinal detachment rather than a serous PED. Fluorescein angiographic findings showed different intensity of fluorescence in the area of PDPM among patients. These findings might be attributable to differences in the nature of the fluid within PDPM or differences in the condition of RPE cells overlying PDPM.

A difference between our study and Freund's study was the high prevalence of visual field defects among highly myopic eyes with PDPM in our study. In our study, glaucomatous visual field defects were detected in 22 of 31 eyes (71.0%), which were examined by Goldmann visual field perimetry. Humphrey visual field testing confirmed the abnormal results in some of these patients. The prevalence of visual field defects in eyes with PDPM was significantly higher

than that in eyes without PDPM. In contrast, Freund et al.[7] reported no peripapillary visual field defects in four patients who had previous visual field testing (Humphrey 30-2). It is unclear why the visual field results were markedly different between the two studies. Because more widespread PDPM was detected in our patients, our study might have included more advanced PDPM cases. The possible mechanism of the concomitant visual field defects in the eyes with PDPM is not clear; however, most of the eyes with PDPM had tilted discs and a deeply excavated myopic conus inferior to the optic disc. These findings suggest that the distorted structure of the neurosensory retina caused by marked tilting of the optic disc and steep excavation of the inferior myopic conus rather than PDPM itself might cause subsequent mechanical damage to the neurosensory retina. This hypothesis might be supported by the finding that the dominant location of visual field defects and PDPM lesions sometimes does not match, as in Case 4. The clinical diagnosis of glaucoma is sometimes difficult to make in highly myopic eyes because of anomalous optic disc changes and atypical visual field changes. Although there is some possibility that the visual field defects observed in the present study were not caused purely by glaucoma, this study suggests that the presence of PDPM might be a novel sign that indicates the existence of concomitant visual field defects in highly myopic patients.

From the retrospective review of serial photographs taken, no changes were noted in the size and shape of PDPM in any of the patients. Freund et al.[7] described one patient with a

progressive involution of the PDPM in both eyes during a 15-year follow-up. In our study, there were no patients with involuted PDPM. The long-term course of PDPM should be investigated to determine whether PDPM eventually regresses.

In conclusion, we evaluated the prevalence and characteristics of PDPM in a large series of highly myopic patients. Although its pathogenesis and pathologic significance remains to be clarified, PDPM might be another indicator for the development of visual field changes in high myopia.

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