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CLINICAL INVESTIGATION

National survey of pellucid marginal corneal degeneration in Japan

Jun Shimazaki[1,2] · Naoyuki Maeda[3] · Osamu Hieda[4] · Yuichi Ohashi[5] · Akira Murakami[6] · Kohji Nishida[3] · Kazuo Tsubota[2] · Japan Pellucid Marginal Corneal Degeneration Study Group

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Abstract
Purpose A national survey was conducted in Japan to analyze the clinical characteristics of pellucid marginal corneal degeneration (PMD).
Methods A questionnaire was sent to all members of the Japan Cornea Society requesting demographic and clinical findings on PMD patients who had been examined between 2008 and 2010. The presence of band-shaped peripheral corneal thinning, detected by slit-lamp biomicroscopy or by a pachymetric map, was set as the diagnostic criterion of PMD.
Results Most of the participating facilities relied on either slit-lamp biomicroscopy or corneal topography as diagnostic tools for the detection of PMD. Data on 347 patients (579 eyes) were returned from the participating facilities for analysis, among which 162 eyes in 84 men and 24 women, with a median onset age of 37 years, met the PMD criteria. Of the 108 patients (162 eyes) with classical PMD, unilateral involvement was found in 25 % of patients (27 eyes). In 17 of the 27 eyes for which topographic findings for the contralateral eye were available, seven eyes were either keratoconus or had a suspected diagnosis of keratoconus. An association with allergic disease was found in 24 eyes (22.2 % of patients). Approximately half of the patients had 1.0 or better spectacle-corrected distance visual acuity, and only 5 % showed 0.1 or worse. The mean keratometric value was 45.7 diopters. On corneal topography, 100 eyes (61.7 %) showed the topographic "crab-claw pattern," and the remaining eyes showed other patterns, including inferior steepening (22.2 %) and an irregular pattern (10.5 %).
Conclusions We conducted the largest clinical survey of PMD to date and found a male predominance, a relatively high prevalence of unilateral involvement, and associated allergic diseases.

Keywords Pellucid marginal corneal degeneration · Corneal topography · Diagnostic criteria

✉ Jun Shimazaki
jun@eyebank.or.jp

[1] Department of Ophthalmology, Tokyo Dental College, 5-11-13 Sugano, Ichikawa, Chiba 272-8513, Japan

[2] Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

[3] Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan

[4] Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan

[5] Department of Ophthalmology, Ehime University, Matsuyama, Japan

[6] Department of Ophthalmology, Juntendo University, Tokyo, Japan

Introduction

Pellucid marginal corneal degeneration (PMD) is a rare, progressive ectatic disorder characterized by thinning of the peripheral cornea [1]. Although the affected cornea maintains its clarity, patients with PMD suffer from progressive deterioration of vision due to irregular astigmatism. The prognosis of PMD is unsatisfactory. Rigid gas-permeable contact lenses are often prescribed for mildly to moderately affected patients; however, the lens fitting is typically poor due to the abnormal contour of the cornea [2, 3]. Corneal transplantation is a last resort in severe cases, but unlike that in the keratoconus, the clinical outcome is often not satisfactory because the grafting has to be large or eccentric to

cover the affected area of the cornea [1, 4]. Additionally, PMD patients are known to visit refractive centers often because they are not satisfied with glasses or contact lens (CL) correction [5]. Keratorefractive surgery is contradicted in PMD, and misdiagnosed or overlooked cases are sometimes labeled as iatrogenic keratectasia.

Despite the importance of the disorder, the characteristics of PMD are relatively poorly defined. Most publications to date are reports of small case series, and there are only a reports in which a large number of cases are described [4]. Similarities between PMD and keratoconus have been reported, which has been attributed to the absence of firm criteria for each disease entity [6, 7]. The classical hallmark of PMD is band-shaped peripheral corneal thinning associated with protrusion of the adjacent cornea detected by slit-lamp biomicroscopy [1]. Maguire et al. report that the so-called "crab-claw" (or "butterfly") appearance in corneal topography is a valuable objective finding in PMD [8]. This finding illustrates the changes in the corneal contour in PMD, namely, marked flattening of the cornea along the corneal periphery that extends to the mid-peripheral oblique corneal meridians. Although corneal topography is useful for the early detection of PMD, it has also been reported that the "crab-claw" topographic finding is not specific to PMD. Lee et al. report that 31 of the 40 eyes examined in their study that showed the "crab-claw" topographic pattern were not affected by PMD; indeed, 67.5 % were cases of keratoconus [9]. Recent advances in corneal image analysis, such as the use of a Scheimpflug-based topographer, slit-scanning topographers, corneal tomography, or anterior segment optical coherence tomography (AS-OCT), provide more detailed information, including information on the corneal posterior curvature and pachymetric mapping.

Here, we report the results of a national survey in Japan and propose diagnostic criteria for PMD. The aims of this study were: (1) to investigate the demographic and ophthalmic characteristics of PMD and (2) to evaluate the current diagnostic criteria used in general practice.

Methods

Subjects and methods

The study was conducted as part of a research grant from the Health and Labor Sciences Research Grants (H22-Nanchi-Itsupan-199) over a period of July 2010 to March 2011. The Japan Pellucid Marginal Corneal Degeneration Study Group was formed specifically to conduct this national survey. A questionnaire was sent to all members of the Japan Cornea Society with the approval of the Japan Cornea Society Board of Directors. The contents of the questionnaire are shown in Table 1. Electronic files on each patient's corneal topography and/or tomography data were returned along with the answers to the questionnaire. The survey covered demographic and clinical findings in PMD patients who were examined between 2008 and 2010. Apart from the questionnaire, the study group did not set any criteria for PMD because the primary aim was to collect as much data as possible to study the diagnostic criteria currently used in general practice; thus, the diagnosis of PMD was left to the judgment of each participating physician. Eyes that had corneal diseases other than PMD and its related conditions, such as overlapping cases with keratoconus, were excluded from the analysis. Eyes that had a history of corneal surgery were excluded from the topographic and refractive analysis unless preoperative data were available. The approval by the Institutional Review Board of the Tokyo Dental College was not required according to the agreement of the committee in the period this study was conducted.

Table 1 Contents of the questionnaire

Contents of the questionnaire
1. Demographic data
Age
Sex
Residence
Onset
Monocular/binocular involvement
Associated systemic diseases including allergic diseases
Family history
History of other ocular diseases
History of ocular surgeries
2. Ophthalmic findings
Visual acuity (uncorrected/spectacle-corrected)
Refraction
Main vision correcting devise
Keratometry
Slit-lamp findings
Corneal topography (axial power map)
Corneal pachymetry
Corneal endothelial density
Corneal aberrometry
Instruments used for corneal topography, pachymetry, specular microscopy, and aberrometry

Analysis of data

One of the study group members (J.S.), who was blinded to demographic and ophthalmic data, categorized the findings of the anterior corneal topography into four patterns: "crab-claw" pattern, inferior steepening, irregular pattern, and other. Consultations with other members of the study

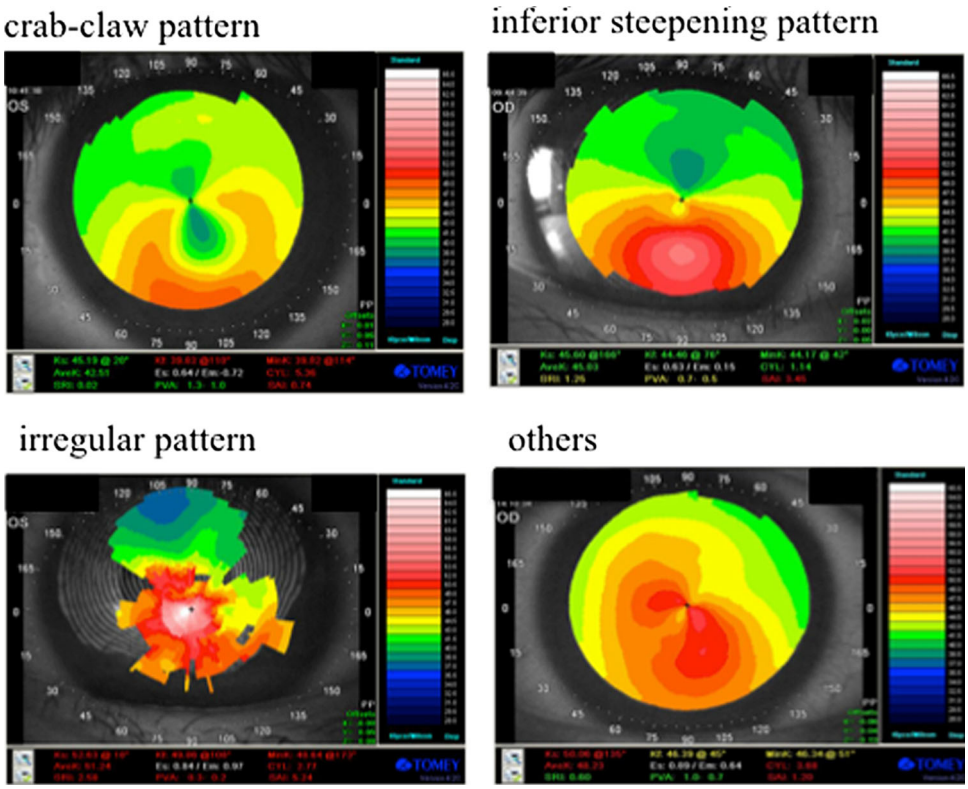

Fig. 1 Representative photographs of corneal topography

group were conducted when necessary. Representative pictures of each pattern are shown in Fig. 1.

The presence of band-shaped peripheral corneal thinning is considered to be the classical hallmark of PMD. Therefore, we defined the presence of inferior thinning, detected by slit-lamp biomicroscopy or pachymetric mapping, as a firm definite criterion of PMD and called cases thus defined as "classical PMD". We examined the demographic and ophthalmic profiles of these patients, and compared them with those of other cases. The association between the diagnosis of PMD and topographic patterns was also studied.

Statistical analysis

Data were presented as the mean ± standard deviation. One-way analysis of variance was used for comparisons among subgroups of patients. Student's *t* test was used to compare continuous variables among the groups. InStat 3 (GraphPad Software, La Jolla, CA) was used for the statistical analyses.

Results

Data collection and demographics

We received responses from 30 medical facilities in the national survey, namely, 13 university-based hospitals, one general hospital, ten private hospitals/clinics, and six refractive centers/CL clinics. Refractive centers and CL clinics reported larger numbers of patients (mean 26.0 and 79.0 patients per center and clinic, respectively) than other facilities (mean 5.8 patients per facility). In all, data on 347 patients (579 eyes) were collected and returned for analysis. The demographic profile of these patients is shown in Table 2. There were 262 men and 85 women, with a mean age of 39.0 ± 10.4 (range 18–78) years. Ocular comorbidities included cataract (12 eyes), glaucoma (11 eyes), vitreoretinal disease (4 eyes), and others (13 eyes). No eyes had a history of keratorefractive surgery. These cases were subcategorized into those of classical PMD (162 eyes of 108 patients), suspected PMD (280 eyes of 161 patients), and other (137 eyes of 78 patients) according to the diagnostic criteria described in the following sections.

Examinations applied for the diagnosis of PMD

Corneal topography was performed in all cases. An axial power map of the topography was used for the analysis when available. Among the four topographic patterns defined among all patients, the "crab-claw" pattern was most common (380 eyes, 65.6 % of patients), followed by inferior steepening (123 eyes, 21.2 % of patients). Specular microscopy was performed in 384 eyes (66.3 %) and aberrometry in 177 eyes (30.6 %). Corneal pachymetry was performed in 461 eyes (79.6 % patients) using an ultrasonic pachymeter (30 eyes), specular microscopy (59 eyes), a slit-scanning

Table 2 Demographic and clinical data for each pellucid marginal corneal degeneration subcategory

Demographic and clinical data	Entire study group	Classical PMD	Suspected PMD	Other ocular comorbidities	*P* value[a]
Number of patients (number of eyes)	347 (579)	108 (162)	161 (280)	78 (137)	
Age (years, mean ± SD)	39.0 ± 10.4	39.4 ± 12.6	39.0 ± 9.35	36.7 ± 10.0	0.18
% Male	75.5 %	77.8 %	75.8 %	71.8 %	0.64
Unilateral involvement[b]	114 (32.9 %)	27 (25.0 %)	51 (31.7 %)	33 (42.3 %)	0.21
Allergic diseases[c]	108 (31.1 %)	24 (22.2 %)	55 (34.2 %)	24 (30.8 %)	0.44
Onset (median, years)	38	37	37	39	
Mean SCDVA, logMAR (decimal)	−0.14 ± 0.36 (0.73)	−0.18 ± 0.39 (0.66)	−0.12 ± 0.30 (0.76)	−0.13 ± 0.42 (0.74)	0.26
<0.5[c]	89 (15.4 %)	32 (19.8 %)	34 (12.1 %)	23 (16.8 %)	0.089
% HCL wearing	59.9	71.0	56.4	54.0	0.0029
Topographic patterns (% of patients)					
Crab-claw	65.6	61.7	100	0	
Inferior steepening	21.2	22.2	0	63.5	
Irregular	4.5	10.5	0	6.6	
Others/unknown	8.6	7.4	0	29.9	

PMD Pellucid marginal corneal degeneration, *SD* standard deviation, *SCDVA* spectacle-corrected distance visual acuity, *HCL* hard contact lens

[a] Difference among the three subcategories (classical PMD, suspected PMD, and others)

[b] Data are presented as the number of cases, with the percentage of patients in parenthesis

[c] Data are presented as the number of cases (%) that had less than 0.5 SCDVA, with the percentage of patients in parenthesis

topographer (52 eyes), a Scheimpflug-based topographer (171 eyes), or AS-OCT (149 eyes). Consequently, information regarding the distribution of corneal thickness (a pachymetric map) was available for 372 eyes (64.2 %).

Diagnostic criteria of PMD

The combination of a slit-lamp examination and corneal topography was the leading method used for diagnosing PMD. Most of the pachymetric maps failed to detect the thinning area because of an insufficient examination diameter, indicating its limited usefulness as a diagnostic tool. The presence of inferior thinning detected by slit-lamp biomicroscopy or a pachymetric map (classical PMD) was observed in 162 eyes (28.0 %) in 108 patients. Of the remaining eyes, 280 eyes in 161 patients (48.4 %) were diagnosed as PMD based on the presence of the "crab-claw" pattern on corneal topography with no evidence of peripheral corneal thinning; these patients were classified into the category "PMD suspects". The other 137 eyes in 78 patients had neither peripheral corneal thinning nor a "crab-claw" topographic pattern, and they were classified as "others".

Characteristics of classical PMD

Demographic characteristics of the "classical PMD", "PMD suspect", and "others" are shown in the Table 2. The classical PMD group comprised 84 men and 24 women with a mean age of 39.4 ± 12.6 years. The median age of onset was 37 years. In 25 % (27 eyes) of the patients, only one eye had PMD, while the other eye did not. In 17 of the 27 eyes for which topographic findings for the contralateral eye were available, ten eyes were normal, two eyes had a suspected diagnosis of keratoconus, and five eyes had a definite diagnosis of keratoconus. An association with allergic disease was found in 24 eyes (22.2 % of patients). Regarding the optical correction devices used, 71 % of the patients (115 eyes) had rigid gas-permeable contact lenses for optical correction, followed by special hard contact lenses (21 eyes, 13.0 %), glasses (13 eyes, 8.0 %), and soft contact lenses (7 eyes, 4.3 %). Four eyes (2.5 %) had a history of corneal surgery, including penetrating keratoplasty (three eyes) and deep anterior lamellar keratoplasty (one eye). We used preoperative ophthalmic data for four eyes subjected to corneal surgery for analysis.

Regarding the ophthalmic findings of the eyes with classical PMD, approximately half of the patients had 1.0 or better spectacle-corrected distance visual acuity (SCDVA), and only 5 % had 0.1 or worse (Table 3). Refractive data were available for 135 eyes, and the vast majority of these eyes showed moderate-to-high myopia in their spherical equivalent (median −5.0 D) (Table 4). Many of the eyes had a relatively high degree of refractive astigmatism (median −3.75 D), and 50 eyes (41.7 %) had ≥5 D of astigmatism (Table 5). The mean keratometric value was 45.7 ± 5.87 D. The 120 of 162 eyes for which

Table 3 Distribution of best spectacle-corrected visual acuity in eyes with classical pellucid marginal corneal degeneration

SCDVA[a]	Number of eyes[b]	% of eyes
≥1.0	80	49.7
0.8–0.9	23	14.3
0.5–0.7	26	16.1
0.1–0.4	24	14.9
<0.1	8	5.0

SCDVA Spectacle-corrected distance visual acuity

[a] Note that more than one-half of the eyes had ≥1.0 vision

[b] One eye was not available for SCDVA data

Table 4 Distribution of spherical equivalents in eyes with pellucid marginal corneal degeneration

Spherical equivalent (D)	Number of eyes[a]	% of eyes
≥0	12	8.9
>−3	17	12.6
>−6	45	33.3
>−9	35	25.9
>−12	15	11.1
<−12	11	8.1

[a] The majority of eyes had moderate-to-high degrees of myopia

Table 5 Distribution of refractive astigmatism in eyes with pellucid marginal corneal degeneration

Refractive astigmatism (D)	Number of eyes[a]	% of eyes
≤1	4	3.3
<2	8	6.7
<3	12	10.0
<4	20	16.7
<5	26	21.7
<6	17	14.2
<7	10	8.3
<8	11	9.2
<9	3	2.5
<10	5	4.2
≥10	4	3.3

[a] Astigmatism data was not available in 42 eyes

data were available on the refractive cylinder axis were divided into three categories based on the axis of the steep meridian: (1) "against the rule" (steep axis 0 ± 20°), (2) "with the rule" (steep axis 90 ± 20°), and (3) "oblique axis" (steep axis 45 ± 20° or 135 ± 20°). Eyes with against-the-rule astigmatism were the most common (73 eyes, 60.8 %), followed by oblique axis (41 eyes, 34.2 %).

On corneal topography, 100 eyes (61.7 % of patients) in the classical PMD category showed the "crab-claw" topographic pattern, and the remaining eyes showed other patterns, including inferior steepening (22.2 %) and an irregular pattern (10.5 %) (Table 2). A representative case of advanced PMD demonstrating the inferior steepening topographic pattern is shown in Fig. 2.

The eyes with classical PMD were subdivided into two groups based on the SCDVA (≥1.0 and <1.0), and the demographic profile and ophthalmic findings in each subgroup are illustrated in Table 6. There were no significant differences in any parameter, including the mean spherical equivalent and topographic patterns.

Comparison between classical PMD and other subgroups

There were no significant differences among the three groups in terms of demographic or ophthalmic findings, except for the rate of hard CL wearing (Table 2). However, when the prevalence of unilateral and bilateral cases in the different subcategories was compared, there was a higher prevalence of "classical PMD" and a lower prevalence of "other" among the bilateral cases (Chi-square test, $P = 0.048$).

Discussion

Pellucid marginal corneal degeneration is typically described as a bilateral, clear, inferior, peripheral corneal thinning disorder characterized by a narrow band of corneal thinning separated from the inferior limbus by a relatively uninvolved area 1–2 mm in width. The etiology of PMD is unclear, and no diagnostic criteria have been established. Indeed, the overlap of PMD with other diseases, particularly with keratoconus, has been a subject of some controversy [1, 10, 11]. There are few large-scale reports of PMD, and the present study is the largest to date. We used the classical criterion for PMD diagnosis, as the presence of these conditions detected either by slit-lamp biomicroscopy or pachymetric mapping is believed to be of definite diagnostic value. In our study, this "classical PMD" sign was seen in 162 eyes.

Demographic characteristics of PMD

We found that several findings in the "classical PMD" cases have not been described previously. First, our data revealed that there was a male predominance of the disease; that is, approximately three-quarters of the patients were men. There has been some controversy regarding a sex predilection in PMD, with some studies reporting no sex difference [1, 10, 11], while others reporting a male predominance [3, 4, 12]. Sridhar et al. reported that 77.6 % of the PMD

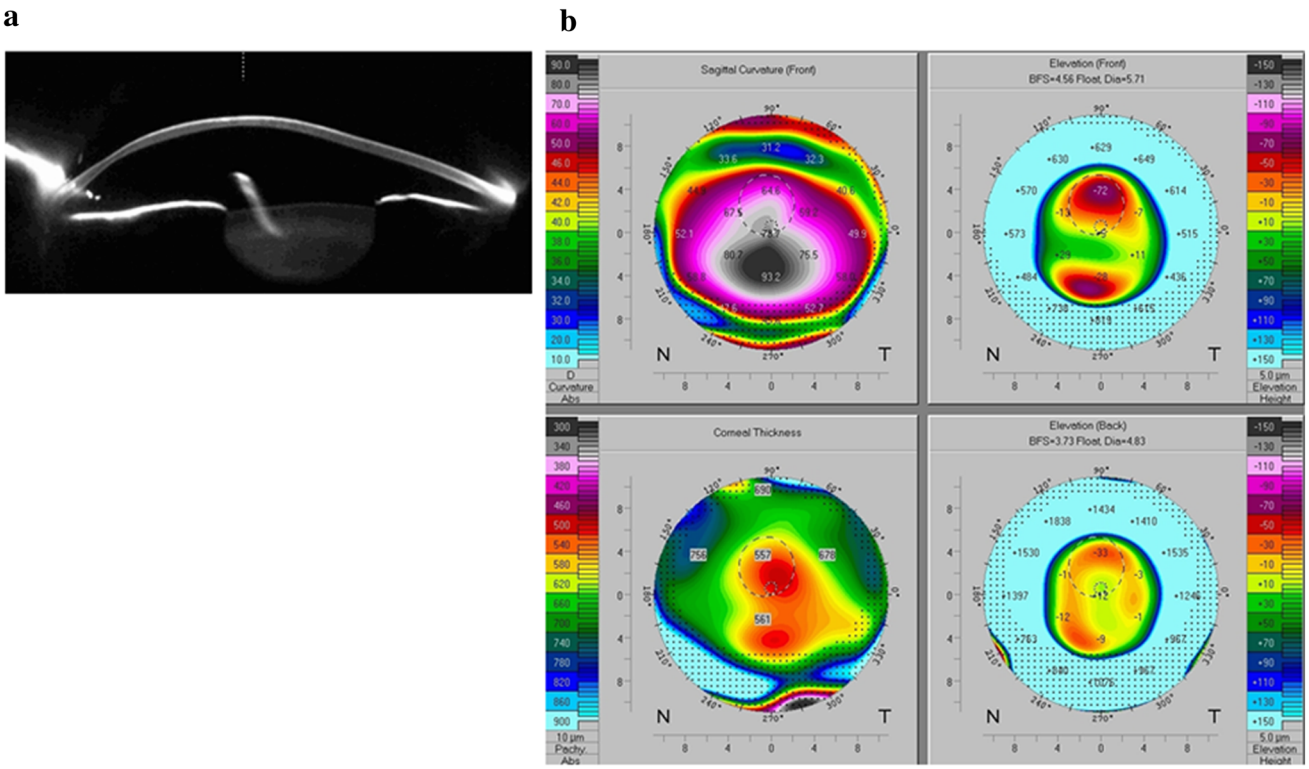

Fig. 2 Corneal contour, topography, and pachymetric map of a 50-year-old man with pellucid marginal corneal degeneration. **a** The corneal tomographic picture demonstrated a typical "beer-belly" pattern with peripheral thinning. **b** Anterior corneal topography showed the "inferior steepening" pattern

Table 6 Demographic and ophthalmic findings of classical pellucid marginal corneal degeneration with and without a spectacle-corrected distance visual acuity of ≥1.0

Demographic and ophthalmic findings	Classical PMD with ≥1.0 SCDVA	Classical PMD with <1.0 SCDVA	*P* value
Number of cases[a] (number of eyes)	39 (80)	56 (81)	
Male:female	30:9	46:10	0.61
Onset (years, median)	38.0	34.5	0.27
Spherical equivalent (diopters, mean ± SD)	−3.4 ± 3.2	−5.2 ± 6.7	0.22
Refractive astigmatism (diopters, mean ± SD)	−4.8 ± 2.3	−4.7 ± 2.3	0.87
Correction with HCL[b]	62 (77.5 %)	52 (64.2 %)	0.083
Topographic patterns[b]			0.69
Crab-claw	50 (62.5 %)	49 (60.5 %)	
Inferior steepening	19 (23.8 %)	17 (21.0 %)	
Others	11 (13.8 %)	15 (18.5 %)	

[a] Bilateral PMD cases with ≥1.0 SCDVA in one eye and <1.0 in the other eye were excluded from the demographic analysis

[b] Data are presented as the number of eyes with the percentage of eyes given in parenthesis

patients in their study were men [4]. Second, our series demonstrated that a considerable number of patients (25 %) had unilateral involvement. Although there are sporadic reports of unilateral PMD [13, 14], such a high rate has not been described previously. While the patients with unilateral and bilateral involvement were similar in age ($P > 0.05$), they did differ according to sex (more men in unilateral cases) and association with allergic diseases (more allergy in bilateral cases). These differences suggest that the patients with unilateral/bilateral involvement have a different disease background. Third, we found that approximately one-fifth of the patients had allergic disorders, such as atopic dermatitis, allergic rhinitis, and conjunctivitis. Such an association has only rarely been reported [15].

Topographical findings of PMD

We noted that eyes with "classical PMD" did not always show the "crab-claw" topographic pattern. We also noted that many of the patients were diagnosed using the corneal topography findings. Many physicians rely on the "crab-claw" curvature pattern seen on anterior curvature maps to confirm the diagnosis. Although the "crab-claw" appearance is a typical topographic finding in PMD [8], it is also observed in other disorders, such as keratoconus [9]. Indeed, only 62 % of the eyes with classical PMD had the "crab-claw" pattern, and more than one-third of the eyes showed some other topography, such as inferior steepening or irregular patterns (Table 6). This finding is consistent with Fuchihata et al., who report that the most common topographical pattern in PMD was the crab-claw pattern (78 %), followed by the inferior steepening pattern (18 %) [16]. It seems likely that the "classical PMD" eyes represent advanced cases, and the corneal contour changes cover the entire inferior cornea; consequently, the anterior curvature tends to be irregular.

Visual function of PMD

Clinically, many patients with PMD seek ophthalmic examinations due to unsatisfactory visual performance. By contrast, PMD patients with good SCDVA would be diagnosed when they visit refractive/CL centers. The former constitute a subgroup of "typical PMD" or "PMD with visual disturbances" in which the eyes show classical PMD findings and a SCDVA of <1.0, while the latter constitute "PMD without visual disturbances". Our results demonstrate that approximately half of the patients included in our study had SCDVA of ≥ 1.0, which might be attributable to the fact that the diseased area was located outside the visual axis. The relatively good vision in patients with PMD indicates that proper screening in refractive centers is even more important than for those with keratoconus. Interestingly, both patients with and those without decreased vision had similar demographic and ophthalmic findings, including refractive condition and topographic patterns (Table 6). These results indicate that the above-mentioned characteristics of PMD are applicable, irrespective of the disease severity, and that all ophthalmologists should be aware of them.

Relationship between PMD and keratoconus

It is conceivable that some patients in our series fell into the category of overlap with keratoconus. We found that seven of 17 patients with unilateral PMD had either keratoconus or were suspected of having keratoconus in the contralateral eyes. In addition, a relatively large proportion of patients showed characteristics typical of keratoconus, such as a male predominance and association with allergic diseases. Unilateral involvement is seen in 1.8–13.2 % of cases of keratoconus [17–20], and the high unilateral rate in our study might have been due to the inclusion of keratoconus cases. However, such "contamination" would not be common in the "classical PMD" group because these patients had advanced disease, many of them showing peripheral corneal thinning by slit-lamp biomicroscopy. Therefore, the above-mentioned clinical characteristics, such as male predominance and a relatively high prevalence of unilaterality, would be true in PMD. The other intriguing finding was that approximately 40 % of the eyes with unilateral PMD had keratoconus or suspected keratoconus. This might be due to the presence of an "overlapping case" of PMD and keratoconus.

Limitations and future studies

This study had several limitations. Most of the patients in our series underwent relatively extensive ophthalmic examinations. In addition to slit-lamp biomicroscopy, corneal topography was performed in 100 % of the patients, and data on the corneal pachymetric distribution and posterior corneal contour were available in approximately two-thirds of the patients. However, the area analyzed in the pachymetric map examination typically ranged from approximately 6 to 9 mm in diameter, which seemed insufficient to detect peripheral corneal changes in PMD. As a result, some of the mild PMD cases might not have been diagnosed correctly, and a number of them might have been underestimated. Recent reports suggest that analysis of the posterior corneal curvature or large-diameter pachymetric mapping is useful for the proper diagnosis of PMD [21, 22]. Such new approaches might be useful for determining the indications for recently developed treatments for PMD, including collagen cross-linking and intrastromal ring segment implantation [23, 24]. The other drawback of our study is that it was a clinic- and hospital-based—not population-based—survey. The demographic and clinical characteristics of PMD shown in this study must be substantiated by a population-based survey. However, such a survey would not be realistic considering the low prevalence of PMD in the general population.

In summary, we report the results of a large-scale clinical survey in Japan and proposed diagnostic criteria for PMS. We noted previously unveiled characteristics, such as male predominance, a relatively high prevalence of unilateral involvement, and association with allergic diseases. Anterior corneal topography was shown to be ineffective in detecting PMD. By analyzing data from these eyes, we will be able to establish more refined criteria that assist in the early detection of PMD.

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