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Review article

Pellucid marginal degeneration: Detection, discrimination from other corneal ectatic disorders and progression

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ABSTRACT

Pellucid marginal degeneration (PMD) is a non-inflammatory ectatic corneal disease characterized by a narrow band of corneal thinning separated from the limbus by a relatively uninvolved area 1–2 mm in width. It is a rare corneal disorder that shares many clinical characteristics with other corneal ectasias, such as keratoconus, keratoglobus or Terrien marginal degeneration. PMD usually starts later in life than keratoconus and progresses slower than keratoconus. Slit-lamp examination is very useful to distinguish PMD from other corneal ectatic disorders with inflammatory nature. Corneal topographic indices and the classical crab-claw topographic pattern cannot be used as the main tool to distinguish between PMD and keratoconus. New Scheimpflug imaging-based devices have shown the importance and usefulness of the pachymetric map for an appropriate diagnosis of PMD. In addition, biomechanical and densitometric properties have been studied as complementary techniques to help in the diagnosis of PMD.

1. Introduction

Pellucid marginal degeneration (PMD) is a non-inflammatory and progressive ectatic corneal disease characterized by a narrow band of corneal thinning separated from the limbus by a relatively uninvolved area 1–2 mm in width [1]. This condition most commonly involves the inferior cornea, with a thinning extending from the 4-o´clock to the 8-o´clock positions [2]. However, there are several reports showing PMD cases with involvement of superior [3,4], and even temporal [5,6] and nasal [6] regions of the cornea. The term "pellucid" means clear and was used by the first time by Schlaeppi [7] to denote the clarity of the cornea and the absence of any scarring, lipid deposition or vascularization, despite the presence of ectasia.

The incidence or prevalence of PMD is not clearly reported in biostatistical studies. Furthermore, it may be considerably underestimated because PMD is often misdiagnosed as keratoconus due to its close resemblance in the clinical presentation. [8,9] According to epidemiological studies about the incidence of PMD, this condition is considered as a rare condition, less common than other ectatic diseases, such as keratoconus, but more common than others, such as keratoglobus or posterior keratoconus [10].

2. Etiologic and heritance factors

Currently, the exact etiology of PMD is unclear and it is not known whether PMD, keratoconus and keratoglobus are distinct diseases or represent different clinical presentations of the same underlying disease. [11,12] Several authors [13,14] have proposed that PMD is a peripheral form of keratoconus due to the close similarities between both conditions [2,15,16]. However, there are some disagreements between both conditions, such as age of presentation. PMD is usually diagnosed in the later decades of life (between the second and the fifth) [3,11] compared to keratoconus (between the puberty and the third decade of life) [17]. Even, several reports have showed PMD cases diagnosed over 60 years old [18], and extraordinarily over 80 years old [19].

In addition, PMD seems to progress slower than keratoconus, presenting less visual alteration over time, [20,21] and lower incidence of corneal hydrops compared to keratoconus [22,23]. In most of cases, the presence of corneal perforation is associated to eye rubbing and/or some degree of potential trauma to the corneal surface [24].

There is strong evidence about the association between keratoconus and systemic disorders. The link between atopic disease, Down´s syndrome, connective tissue diseases and other systemic diseases with keratoconus was reported more than 30 years ago. [11,17] However,

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fewer studies exist to date correlating the presence of PMD with systemic diseases. Fernandez-Barboza et al [25] reported two cases of PMD coexisting with Sjögren syndrome, suggesting a possible association between both conditions. Progressive connective tissue diseases, particularly scleroderma, have been also reported to be associated with PMD [26]. Likewise, Dundar et al [4] reported a case of unilateral superior DMP and ichthyosis associated to chronic eye rubbing. All these findings seem to indicate the presence of a relationship between PMD and systemic diseases associated with eye rubbing, but studies with larger samples should be developed to confirm this assumption.

Unlike in keratoconus, where published reports do suggest an associated inheritance, similar evidence for PMD is lacking [2]. Except for a few reports where topographic abnormalities were found in asymptomatic family members of a patient with PMD [27], there are no indicators of any type familiar association.

Ultrastructural features, such as the architecture of collagen fibrils, proteoglycans and keratocytes have been investigated in PMD, obtaining different concentrations compared to healthy and keratoconic eyes [28]. In the same vein, Pasztor et al. [29] found and reported the presence of biochemical differences between PMD and keratoconus in several tear mediators.

All these discrepancies between keratoconus and PMD suggest that these ectatic disorders may be different manifestations or different phenotypic presentations of the same pathophysiological condition. For this reason, more hystophathological studies are required to understand the origin of ectatic corneal disorders and the differences in their etiology. In spite of this, there are some clinical manifestations that may help in the differentiation between ectatic diseases, including PMD. The identification of the main clinical manifestations of PMD is a crucial issue for a proper diagnosis of this condition, and consequently for a better management of the disease.

3. Typical clinical manifestation of PMD

The hallmark of the disease is an inferior band of thinning 1 to 2 mm from the inferior limbus [2,10], although as previously commented, this band may be located on other positions. Classically, there is a flattening of the vertical meridian above the band of thinning, with the generation of a marked “against-the-rule” astigmatism [14]. Likewise, the cornea frequently presents an area of increased curvature below this band [14]. Therefore, the corneal protrusion in PMD is then placed below the area of thinning, with the thickness of the central cornea normally maintained within the normal range [10,30]. These morphological characteristics generate a typical topographic map, the “crab claw” pattern (Fig. 1). This pattern is also called “butterfly”, “lobster” or “kissing doves” in other well-documented reports [1,15,31,32].

Robin et al. [30] explained that the degree of peripheral thinning is usually severe, resulting in up to 80% stromal tissue loss. Nevertheless, the area between the thinned band-like region and the limbus cornea remains clear, without any scarring, lipid deposit or vascular process [2].

PMD has been considered as a bilateral condition [2], but some authors have also described the occurrence of unilateral cases [4,18,33–35]. No gender predilection has been found in most of published series [2]. However, some articles suggested that more males are affected [35].

It should be considered that not all cases of PMD follow this general clinical pattern, presenting specific differential issues. For this reason, some PMD cases can be confused with others ectatic disorders. Furthermore, other ectatic disorders, such as keratoconus, may show patterns compatible with PMD,8 with the potential of leading to a wrong diagnosis.

4. Differential diagnosis

The differentiation between all ectatic disorders is clinically very relevant [14,36] for a suitable management of each condition. However, it is not always an easy task due to the similarities between some ectatic corneal disorders, especially in atypical manifestations of each of them. In the following lines, the main distinctive features allowing the clinician to distinguish PMD from the rest of ectatic disorders are described in detail.

4.1. Keratoconus vs. PMD

Keratoconus is an ectatic corneal disorder characterized by a progressive corneal thinning that generates a corneal protrusion leading to a conical shape of the cornea, presence of irregular astigmatism and decreased vision. [20] This condition usually begins to develop at puberty and usually progresses quicker than PMD [11]. Its incidence varies depending on some factors, such as the ethnic group of the sample evaluated or the criteria used to establish the diagnosis. However, this incidence is greater than that corresponding to PMD [17].

Corneal protuberance and stromal thinning are appreciated in moderate and advanced stages of keratoconus on biomicroscopic examination [37]. Also, Fleischer ring and even Vogt's striae are observed in all clinical forms of keratoconus [17,38]. However, these signs are difficult to be found in very early stages. In these cases, and mainly in preclinical stages of the disease (“subclinical keratoconus” - “keratoconus suspect” - “frustre keratoconus”), in which visual abilities are not

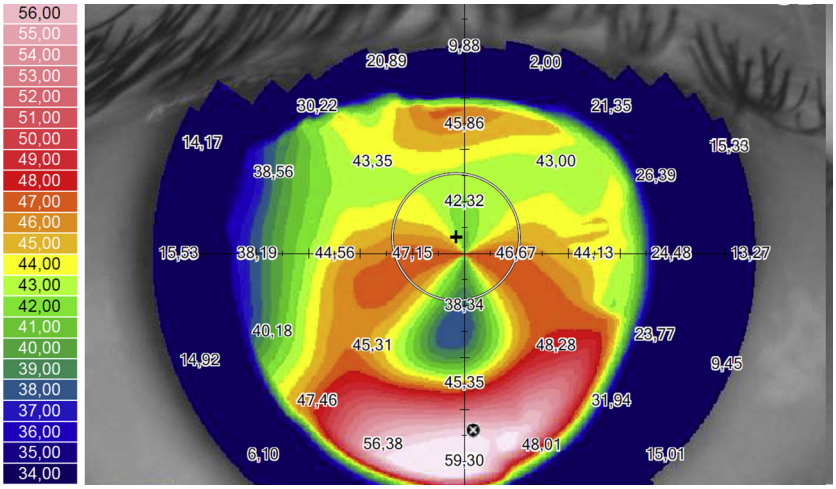

Fig. 1. Tangential anterior curvature map of a pellucid marginal degeneration (PMD) obtained by a rotating Scheimpflug device (Sirius; *Construzione Strumenti Oftalmici, Italy*). It shows the classic “crab-claw” pattern.

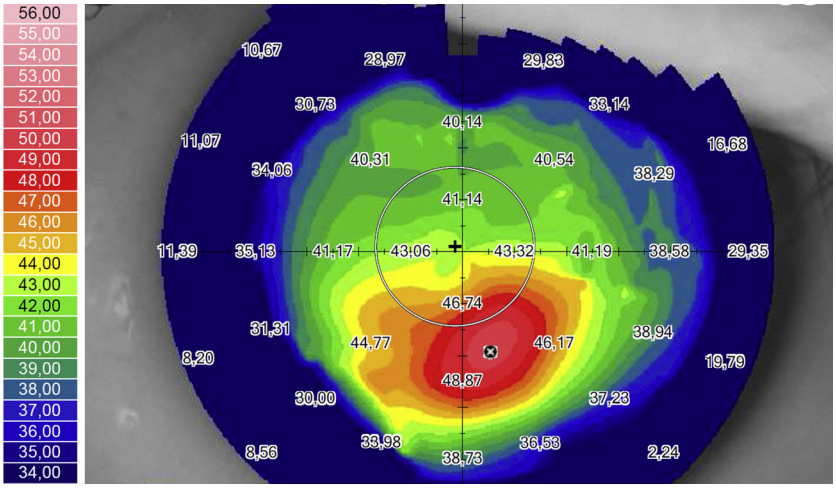

Fig. 2. Tangencial anterior curvature map of a keratoconic cornea obtained by a rotating Scheimpflug device (Sirius; *Construzione Strumenti Oftalmici, Italy*). It shows the protrusion in a classic circular/oval pattern.

affected, corneal topography system is the main tool to obtain a proper diagnosis. This test allows the clinician to detect the presence of conical protrusion and infero-superior topographic asymmetry that are typical signs of keratoconus [20,37,39,40].

Classic pattern of keratoconus is the presence of a well-delimited zone with a high dioptric value, surrounded by progressively decreasing curvature zones [37]. The shape of this conical protrusion is normally circular or oval (Fig. 2), being mainly located on the center of the cornea or slightly displaced to the inferior cornea. However, the development of superior keratoconus has been also reported in some studies, and therefore the conus location is not an accurate enough criterion for diagnosing this corneal degeneration. In addition, the corneal protrusion may be also manifested in an asymmetric bow-tie pattern, as shown in Fig. 3 [40]. Moreover, keratoconus may present a "crab-claw" pattern in the topographic map, such as happens in PMD. This kind of keratoconus is denominated in some series [8] as "pellucid-like keratoconus" (PLK), with the potential of being easily misdiagnosed as a true PMD in the clinical practice. This shared characteristic justifies the use of other tools to obtain a proper differential diagnosis between both conditions. In the following lines the main distinctive features between keratoconus and PMD are explained, including slit-lamp signs, topographic parameters, pachymetric data, high order aberrations, corneal densitometry and the biomechanical response of the cornea (Table 1).

4.1.1. Slit-lamp examination

Fleischer ring, Vogt striae and stromal tissue with conical protrusion are typical signs observed on biomicroscopic or slit-lamp examination in moderate and advanced keratoconus. [11,17,37] Indeed, the presence of these biomicroscopic signs was the first criterion established for keratoconus diagnosis [11]. In more advanced cases, subepithelial fibrillary lines, prominent nerves and scarring of Bowman`s membrane can be detected on slit-lamp examination [17]. However, PMD rarely presents these findings, being differential factors to distinguish both conditions in a large amount of patients, especially in moderate or advanced cases [10]. The major limitation of using slit-lamp examination for differentiating between keratoconus and PMD is in the detection of early or even subclinical stages of the diseases, because these are not associated to biomicroscopic signs or these signs are imperceptible [1]. In such conditions, other diagnostic tests and examinations are required to confirm the potential presence of an incipient ectatic condition. Another limitation is the incapacity to measure and quantify objectively the degree and location of the thinning, which is the main clinical key to distinguish both entities. Some criteria have been established to estimate the borderline in pachymetric terms between PMD and keratoconus using slit lamp biomicroscopy [13]. This have been done by comparing the location of the thinning with the pupil margin, being a very subjective criterion and dependent on many physiological factors.

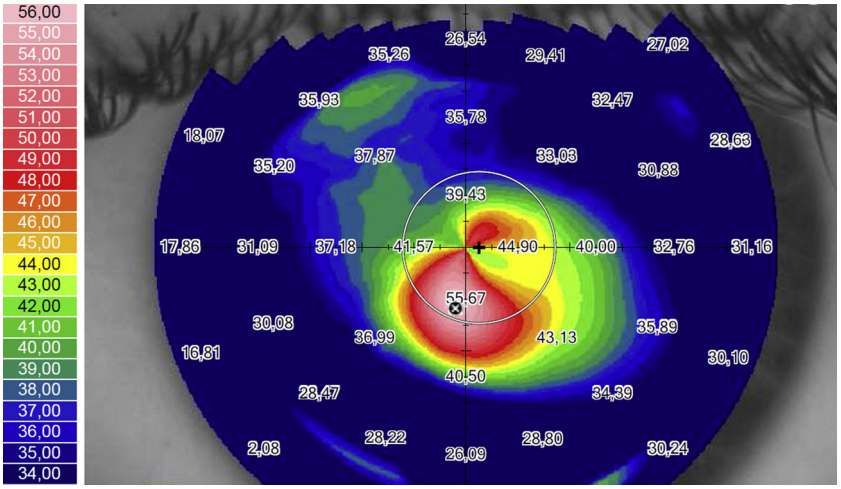

Fig. 3. Tangencial anterior curvature map of a keratoconic cornea obtained by a rotating Scheimpflug device (Sirius; *Construzione Strumenti Oftalmici, Italy*). It shows the protrusion in a bow-tie pattern.

Table 1
Main distinctive clinical features between keratoconus and PMD.

Feature	Keratoconus	PMD
BSCVA reduction [41]	Even in mild stage	Only in moderate or advanced stages
Vogt Striae [42]	Commonly present in moderate and advanced stages	Absence
Fleischer ring [37]	Commonly present in moderate and advanced stages	Absence
Munson sign [37]	Commonly present in moderate and advanced stages	Absence
"Scissors" retinoscopic reflex [10]	Generally present in clinical stages	Absence
Evolution [43,44]	Generally progress quicker	Generally progress slower
Typical presentation [1,10]	Central/paracentral protrusion with central thinning	Peripheral crab claw steepening with peripheral thinning
Incidence [10]	Relatively common	Uncommon

Abbreviations: PMD, pellucid marginal degeneration; BSCVA, best spectacle-corrected visual acuity.

4.1.2. Pachymetric data

The description of the classic band of thinning in PMD by using the slit lamp is not an easy task. For this reason, many eye care practitioners rely on the "crab claw" curvature pattern depicted on anterior curvature maps to confirm the diagnosis [1]. Current studies have analyzed the pachymetric characteristics of ectatic eyes with "crab claw" pattern in the topography map. These studies have demonstrated that "crab claw" patterns may appear in both keratoconus and PMD. Sinjab et al. [8] determined that both keratoconus and PMD may present a "crab claw" pattern in the topographic map. Similarly, Lee et al. [14] analyzed a sample of 40 ectatic eyes with the same pattern, being 9 PMD and 27 PL K. Fuchihata et al. [13] compared the morphological shape in PMD and keratoconus, demonstrating variable shapes in both conditions (central round – central oval – paracentral round – paracentral oval – decentered round – decentered oval). Therefore, considering the topographic pattern as a single diagnostic index in PMD may lead to a wrong diagnosis of this condition and consequently to an inappropriate management. It may be partially attributable to the limitations of obsolete topography systems providing only an analysis of the anterior corneal surface, and not providing pachymetric data of the whole cornea. However, modern tomography devices provide this information, which is of a great relevance to obtain an accurate diagnosis of PMD [45].

The corneal thinning in PMD involves the peripheral cornea and therefore a characteristic pattern called "bell" sign (Fig. 4) may be appreciated in advanced cases of the disease [8]. This sign is characterized by the presence of a maximum thinning in the inferior cornea with a progressive increase of the thickness through central and superior areas. Sinjab et al. [8] suggest that this map is the main tool to distinguish between keratoconus and PMD, especially when a "crab claw" pattern is presented in topographic maps. Likewise, Lee et al. [14] compared the location of the thinnest corneal point from the central cornea in PMD and keratoconus and found a higher displacement of such point in PMD (1.27 ± 0.48 mm keratoconus vs. 2.56 ± 2.56 mm PMD, $p = 0.034$). Koçluk et al. [32] also analyzed the thinnest point displacement in keratoconus and PMD, differentiating x and y coordinates. These authors obtained a higher displacement of the thinnest point in PMD along y-axis (0.70 mm keratoconus vs. 2.17 mm PMD, $p < 0.001$). The distribution of pachymetric data in the main regions of the cornea in PMD and keratoconus has been also analyzed by Tummanapalli et al [9], demonstrating that a higher thinning was present in inferior regions in PMD (513.86 ± 72.96 μm PMD vs. 559.15 ± 48.40 μm keratoconus, $p < 0.05$), whereas a higher thinning was present in the central cornea in keratoconus (449.31 ± 65.01 μm keratoconus vs. 523.00 ± 46.14 μm PMD, $p < 0.05$).

All authors agree in the relevance of pachymetric data for the diagnosis of PMD. Furthermore, most of authors suggest the necessity of a full pachymetric map covering the central 12 mm of the cornea as a mandatory test for a correct diagnosis of PMD. [1]

4.1.3. Topographic parameters

Differences can be found in the orientation of corneal astigmatism when comparing PMD and keratoconus, because PMD is characterized by the presence of marked ART astigmatism due to the flattening of the vertical meridian [1]. However, the presence of ART astigmatism is not a common issue in keratoconus. Therefore, this sign cannot be used a single diagnostic factor for discriminating between PMD and keratoconus. Topographically, Fuchihata et al. [13] reported a greater steepening of the cornea in keratoconic eyes than in PMD eyes (Kmax: 63.0 ± 10.9 D keratoconus vs. 52.1 ± 5.70 D PMD, $p < 0.05$). However, Koçluk et al. [32] found the opposite result (Kmax: 49.7 D keratoconus vs. 54.6 D PMD, $p = 0.009$) and Koc et al. [15] did not find statistically significant differences in keratometric data between both ectatic disorders (Kmax: 50.4 ± 3.2 D keratoconus vs. 51.1 ± 3.2 D PMD, $p = 0.531$). Therefore, corneal power does not seem to be an adequate parameter for discriminating between keratoconus and PMD.

A new method that analyzes the shape of the cornea using fitting two-dimensional Gaussian functions have found differences in some parameters (vertical peak location: −1.10 ± 0.43 mm keratoconus vs. -1.94 ± 0.53 mm PMD, $p = 0.007$), suggesting that cones in PMD are located considerably more inferiorly compared with keratoconus [31]. Similarly, others studies have also reported a higher level of decentration of the corneal steeping zone in PMD than in keratoconus [9,13]. Asphericity (Q) is usually lower in keratoconus than in PMD. Tummanapalli et al. [9] found mean Q of −0.51 ± 0.35 in keratoconus and 0.14 ± 0.24 in PMD ($p < 0.001$), and Koçluk et al [32] found mean Q of -0.54 in keratoconus and 0.09 in PMD ($p < 0.001$). However, Koc et al [15] compared PMD and inferior keratoconus, and did not find statistically significant differences in asphericity data between these two conditions (Q: −0.04 ± 0.37 inferior keratoconus vs. −0.05 ± 0.36 PMD, $p = 0.95$).

Concerning elevation data, several studies [9,14,15,32] have been recently conducted, showing variable results, as displayed in Table 2. Overall, all studies agree in the presence of a higher value of maximum anterior elevation in PMD than in keratoconus, with statistically significant differences between both groups. This confirms that the corneal protrusion in the anterior corneal surface is located more peripherally in PMD than in keratoconus. For the posterior corneal surface, higher values of elevation in PMD than in keratoconus have been reported, but without statistically significant differences between conditions. Therefore, there is no clear consensus about the use of posterior elevation data to discriminate between PMD and keratoconus.

Tummanapalli et al [9] designed a specific index called "PMD index" which was calculated from topographic and pachymetric indices. This index offered a suitable ability to detect PMD cases, distinguishing from healthy eyes and other ectatic corneal disorders (sensibility 93.3%, specificity 90.6%, AUC 0.974, cutoff value > -0.07, $p < 0.0001$).

4.1.4. High order aberrations (HOA)

A few studies [21,46,47] have discussed on HOAs in patients with PMD. Kamiya et al [21] reported a long-term follow-up of a clinical case of PMD. These authors showed that corneal coma-like aberrations increased 1.67-fold (0.473 μm to 0.792 μm) and corneal spherical-like

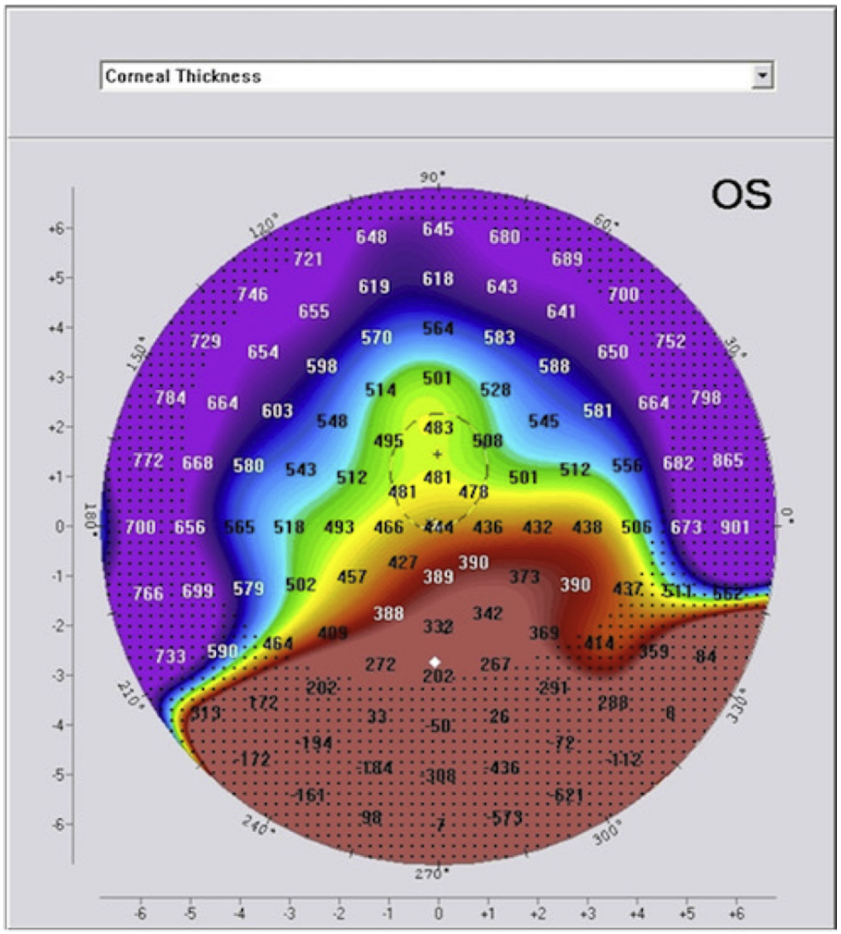

Fig. 4. Corneal pachymetric map of pellucid marginal degeneration (PMD) obtained by a rotating Scheimpflug device (Pentacam HR; *OCULUS Optikgerate GmbH, Germany*). It shows a "bell" sign, which is an indicator of peripheral corneal thinning.

aberration remained almost stable during a 11-year follow-up. Radhakrishnan et al. [46] reported a clinical case of PMD with a full aberrometric examination. These authors found that trefoil was the most relevant HOA, which is a very uncommon finding in keratoconus [48]. Oie et al. [47] reported an analysis of a sample of 20 PMD and 76 keratoconus eyes. These authors obtained higher values of trefoil in PMD than in keratoconus (0.41 µm x 27.1° PMD vs. 0.19 µm x 93.8° keratoconus). However, primary coma values were lower in PMD compared to keratoconus (0.21 µm x 85.5° PMD vs. 0.66 µm x 82.5° keratoconus). Concerning spherical aberration, a trend to more negative values has been reported in keratoconus compared to PMD. In fact, Oie et al. [47] found negative spherical aberration in all cases of a keratoconus samples while only 10% of a PMD sample showed negative spherical aberration.

Definitively, patterns of HOAs are different in PMD compared to keratoconic eyes, possibly due to the difference in the position of the corneal apex relative to the entrance pupil. However, there is no strong evidence to confirm the applicability and suitability of HOAs as a diagnostic tool to differentiate between keratoconus and PMD.

4.1.5. *Corneal biomechanical response*

In keratoconic eyes, significant alterations occur in corneal biomechanical properties, showing a weaker behavior than normal eyes [49]. With the Ocular Response Analyzer (ORA), corneal hysteresis (CH) and corneal resistance factor (CRF) have been shown to be lower in keratoconus compared to normal eyes [49,50]. However, in PMD, few studies have been conducted to analyze the ORA results [51–53], that are summarized in Table 3. According to Sedeghat et al. [51], CH and CRF are lower in PMD than in normal eyes but their values are close to those found in a keratoconus group. Labiris et al. [52] and Lenk et al. [53] also found differences between PMD and healthy eyes in several biomechanical parameters. These authors found differences not only for CH and CRF, but also for the "keratoconus match index", KMI (0.34 ± 0.43 PMD vs. 0.95 ± 0.30 control group; $p < 0.001$),

Table 2
Anterior and posterior elevation data in keratoconus and PMD groups in different studies.

Mean ± SD	Anterior Elevation (µm)			Posterior Elevation (µm)		
	Keratoconus	PMD	p-value	Keratoconus	PMD	p-value
Tummanapalli [9]	47.59 ± 20.23	107.23 ± 82.31	< 0.01	89.56 ± 33.75	146.16 ± 130.64	> 0.05
Lee [14]	57 ± 26	94 ± 60	0.10	115 ± 46	180 ± 99	0.098
Koc [15]	60.8 ± 20.3	84.8 ± 32.9	0.005	97.1 ± 29.5	133.9 ± 50.9	0.004
Koçluk [32]	40	100	< 0.001	61.0	124.0	< 0.001

Abbreviations: SD, standart deviation; PMD, pellucid marginal degeneration.

Table 3
Corneal biomechanic response presented as corneal hysteresis (CH) and corneal resistance factor (CRF) in keratoconic, PMD and healthy eyes.

Mean ± SD	CH (mmHg)				CRF (mmHg)			
	Keratoconus	PMD	Healthy	p-value	Keratoconus	PMD	Healthy	p-value
Sedeghat [51]	8.43 ± 0.78	8.91 ± 1.05	10.89 ± 1.08	< 0.001	7.19 ± 1.11	8.21 ± 1.05	10.69 ± 1.41	< 0.001
Labiris [52]	–	8.39 ± 1.50	10.80 ± 1.77	< 0.001	–	7.83 ± 1.87	10.18 ± 2.08	< 0.001
Lenk [53]	–	8.3 ± 2.2	10.4 ± 2.1	< 0.001	–	7.8 ± 2.4	10.5 ± 2.1	< 0.001

Abbreviations: SD, standart deviation; PMD, pellucid marginal degeneration.

providing a good diagnostic ability (AUC: 94.8, cutoff: 0.626, sensitivity: 85.71%, specificity: 90.1%). These findings suggest that there is an alteration of the ORA biomechanical properties of the cornea in PMD. However, CH and CRF cannot be used as a diagnostic tool to distinguish between keratoconus and PMD.

4.1.6. Corneal densitometry

Several studies [54,55] have reported an increase of corneal densitometry values in keratoconus for central (0–2 mm) and paracentral (2–6 mm) regions of the cornea. These studies associate this alteration to a disruption of epithelial layer structure and stroma, generating light backscatter. Concerning densitometric properties in PMD, only one study has been developed to this date [15]. It compares the corneal densitometry in inferior keratoconus and PMD at three different depths (anterior layer, central layer and posterior layer). Moreover, the densitometric analysis was divided into different concentric zones: central area (2 mm), paracentral area (2–6 mm), and peripheral area (6–10 mm and 10–12 mm). These authors found higher densitometry values in the PMD group for peripheral regions of the cornea in all zones and layers compared to keratoconus group (total densitometry$_{6\text{-}10\ mm}$: 18.22 ± 4.86 PMD vs. 13.81 ± 2.44; $p < 0.001$ // total densitometry$_{10\text{-}12\ mm}$: 23.90 ± 8.97 PMD vs. 19.33 ± 6.17; $p = 0.011$). [15] Therefore, densitometric evaluations may facilitate the differential diagnosis between both conditions, although more consistent studies should be performed to confirm this hypothesis.

4.2. Keratoglobus vs. PMD

Keratoglobus is a bilateral corneal ectatic disorder characterized by a globular protrusion of the cornea associated with diffuse thinning from limbus to limbus. The thinning is commonly maximal at the periphery and may be up to one-fifth the normal corneal thickness. [36,56]. Even, this condition may be associated with scleral thinning, generating a blue sclera [57]. It has non-inflammatory character and therefore patients generally present with clear corneas (without straiae, vascularization, lipid deposition or opacification) unless episodes of hydrops and scarrings occur [56]. However, these corneas are prone to rupture after minimal trauma or even spontaneously [58]. This finding differs from PMD, where corneal perforation is extremely rare [22,23]. Main differences between both conditions are described in Table 4.

Keratoglobus is primarily considered to be congenital, with minimal progression during life [11,56]. However, in more recent years, some reports have been published showing not congenital forms of keratoglobus, with association to disorders of the connective tissue, such as Ehlers-Danlo syndrome, Marfan syndrome and Rubinstein-Taybi syndrome [56]. Karabatsas and Cook [60] reported the association of keratoglobus in one eye with topographic evidence of PMD in the fellow eye. These authors suggest that the natural history of PMD may lead to keratoglobus by circumferential extension of the peripheral corneal gutter. The occurrence of both clinical forms of corneal ectasia in the same patient may reflect the same pathophysiological process but leading to different clinical forms. In the same vein, Rumelt and Rehany [12] reported a case of surgically induced keratoglobus in PMD, supporting the hypothesis that both diseases are different phenotypic manifestations of the same disorder.

Table 4
Main distinctive clinical features between keratoglobus and PMD.

Feature	Keratoglobus	PMD
BSCVA reduction [59]	Only in moderated or advanced stages	Only in moderated or advanced stages
Vascularization [56]	Absence	Absence
Opacification [56]	Absence	Absence
Lipid deposition [56]	Absence	Absence
Corneal hydrops incidence [58]	Common	Rare
Evolution [11]	Progress slowly	Progress slowly
Typical presentation [12,36,56]	Entire cornea	Inferior cornea
Incidence [11]	Uncommon	Uncommon

Abbreviations: BSCVA, best spectacle-corrected spectacle visual acuity, PMD, pellucid marginal degeneration.

Differential diagnosis of keratoglobus with PMD is mainly based on the thinning area: the entire cornea is thinned in keratoglobus, while only a region of the peripheral cornea is thinned in PMD. This appreciation is clearly visible on slit-lamp examination, especially in advanced stages of the disease. However, in doubtful cases, pachymetric maps may allow the clinician to determine the specific region of the cornea presenting the thinning [56].

4.3. Terrien marginal degeneration vs. PMD

Terrien Marginal Degeneration (TMD) is a bilateral peripheral corneal ectasia primarily affecting the superior cornea, which may progress circumferentially. [30,36] This condition is very uncommon and commonly progresses very slowly [61]. It can cause acute ocular inflammation with pain, but this situation is very rare [10]. TMD includes ectasia, thinning band and furrowing of the peripheral cornea with associated lipid deposition, as well as vascularization. Lipid deposition develops along the anterior edge, while vascularization stems radially from the limbus and is located within the anterior stroma [62]. Initial findings present as fine, white-yellow, punctate, stromal opacifications that appear similar to arcus senilis [63]. Table 5 summarizes the main differences between both clinical entities, TMD and PMD.

4.4. Mooren`s ulcer vs. PMD

Mooren`s ulcer is an idiopathic condition characterized by

Table 5
Main distinctive clinical features between TMD (Terrien Marginal Degeneration) and PMD (Pellucid Marginal Degeneration).

Feature	TMD	PMD
Vascularization [62]	Presence	Absence
Opacification [63]	Presence	Absence
Lipid deposition [62]	Presence	Absence
Evolution [36]	Progress very slowly	Progress slowly
Typical presentation [36]	Superior cornea	Inferior cornea
Incidence [36]	Very uncommon	Uncommon

Table 6
Main distinctive clinical features between Mooren`s ulcer and PMD (Pellucid Marginal Degeneration).

Feature	Mooren`s ulcer	PMD
Inflammatory condition [30]	Yes	No
Vascularization [66]	Presence (healing cases)	Absence
Corneal infiltrates [64,66]	Presence	Absence
Epithelial defects [66]	Presence	Absence
Evolution [64]	Changeable	Progress slowly
Typical presentation [64]	Changeable	Inferior cornea
Incidence [65]	Very uncommon	Uncommon

unilateral or bilateral painful, inflammatory corneal thinning and ectasia of the peripheral cornea, although it may progress circumferentially and centrally [30,64]. Epidemiological studies suggest that the disease is rare, especially in the northern hemisphere [65]. Slit-lamp examination signs of Mooren`s ulcer classically include perilimbal corneal infiltrates, epithelial defects within the ulcerated region and the development of a shallow furrow at the edge of the ulcer [46]. The site of involvement is usually the inferior region but eventually it may involves the entire cornea, being potentially variable depending on each particular case [64]. Vascularization occurs during the healing process which can last up to 12–18 months [66].

Therefore, differential diagnosis of PMD versus Mooren`s ulcer should be performed according to slit-lamp examination, which allows the clinician to determine the kind of thinning process (inflammatory vs. non-inflammatory) and to detect biomicroscopic signs previously explained and summarized in Table 6.

5. Subclinical PMD

The corneal thickness is not uniform along the surface, neither pathologic nor healthy corneas. Normally, healthy eyes have the thinnest point located near to the corneal apex, and the corneal tissue is thickening progressively throughout peripheral regions. However, this pattern may be very variable according to each particular case, being difficult to define a normal distribution pattern [67,68].

If the pachymetric data in the peripheral regions of the cornea are not measured, the detection of the presence of a peripheral thinning, which is the main distinctive characteristic of PMD, only using slit lamp examination is a difficult task [2,10]. Advanced cases of PMD can be easily diagnosed as the minimum thickness point (MCT) is located clearly on the periphery and such thinning is visible on slit lamp examination. However, in clinical practice, cases showing MCT located on central or paracentral zones (Fig. 5) can be much more difficult to be detected. In such cases, pachymetric maps show the clinician how thickness in peripheral zones (divided by quadrants) is clearly lower than in the rest of quadrants [8,10,13]. Many reports [13,28] consider these cases as “subclinical PMD” because exist a peripheral thinning (according to the definition) but it is not sufficiently evident to be considered as PMD. However, there is no strong scientific evidence supporting the use of this term of subclinical PMD, being considered these cases by some authors as keratoconus or pellucid-like keratoconus.

6. Progression

The documentation and characterization of PMD progression is scarce, with a low number of studies providing some evidence of how this pathological condition progresses. It is well documented in the scientific literature that PMD usually starts later in life than keratoconus and progresses slower than keratoconus [8,11,17]. Several case reports have considered this pathology as a progressive condition, although the follow-up period is not long enough before the surgical treatment applied [69,70]. Other case series have reported a lower progression capability of PMD compared to keratoconus [21,26]. Even, a case of PMD followed during 11 years has been reported with minimal signs of progression [21]. In addition, as previously commented, the development of corneal hydrops is more uncommon in PMD than in keratoconus [23,25]. These findings suggest that PMD is less progressive than other corneal ectatic disorders, but this assumption should be demonstrated by performing longitudinal studies with large samples. In general, more studies documenting the progression of PMD are still necessary in order to understand better the course of this disease.

7. Conclusion

In conclusion, PMD is a rare corneal disorder which shares many clinical characteristics with other corneal ectasias, such as keratoconus, keratoglobus or TMD. All of these ectatic disorders differ markedly in prognosis and management. For that reason, an accurate diagnosis is crucial for an appropriate management of the disease.

Slit-lamp examination is very useful to distinguish PMD from corneal ectatic disorders with inflammatory nature, like Mooren`s ulcer or TMD in advanced stages. However, the differential diagnosis between

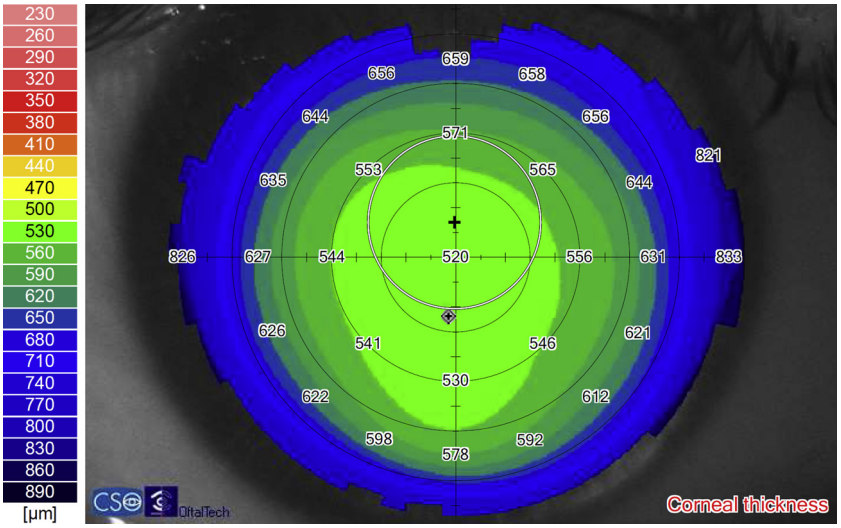

Fig. 5. Corneal pachymetric map of subclinical/early pellucid marginal degeneration (PMD) obtained by a rotating Scheimpflug device (Sirius; *Construzione Strumenti Oftalmici, Italy*). It shows the minimum corneal thickness in the center zone, but the inferior peripheral zone is thinned compared with the others peripheral positions.

PMD and keratoconus is extremely complicated according to biomicroscopic findings, especially in early stages. Therefore, additional examinations are required to distinguish both conditions. Corneal topographic indices and the topographic pattern (crab-claw pattern in PMD) in the tangential and sagittal map have been used in the last decades as the main tool to distinguish between PMD and keratoconus. Despite that, new Scheimpflug imaging-based devices, which analyze both anterior and posterior corneal surfaces and provide thickness measurements in the main regions of the cornea, have demonstrated that PMD can be misdiagnosed with keratoconus only using topographic parameters. Some studies have shown the importance and usefulness of the pachymetric map for an undeniable diagnosis of PMD. In addition, biomechanical and densitometric properties have been studied as complementary techniques to help in the diagnosis of PMD, but more scientific evidence on the use of the techniques must be obtained in the future.

Disclosure

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